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Physiologic and Surgical Considerations in the Treatment of Duodenal Ulcers*

JAMES T. PRIESTLEY,† M.D., *Rochester, Minnesota*

ALTHOUGH duodenal ulcer has been the subject of extensive study for many years, the ideal treatment of this condition still awaits development. During this time many promising ideas have been tried, only to be discarded as time has proved what their actual merit is. Currently, from a surgical viewpoint, vagotomy is the procedure which arouses most interest and discussion. Although this operation is still in the phase of clinical trial, evidence is accumulating which in time will determine its proper place in the treatment of this disease. Because of the chronicity and tendency to recurrence of benign peptic ulceration, years are required, unfortunately, before the efficacy of any treatment of this condition can be accurately evaluated. Initial enthusiasm for any new therapy, either medical or surgical, should always be tempered by consideration of this fact.

All recognized forms of treatment for duodenal ulcer have as their main objective reduction of the "acid-pepsin" factor in gastric secretion inasmuch as convincing evidence, both experimental and clinical, attests the primary importance of this factor in the genesis of duodenal ulceration. Likewise it has been demonstrated that the desirability of any given treatment is dependent on the thoroughness with which reduction of gastric secretion is accomplished and the lack of unfavorable associated effects or sequelae. Medical measures in the treatment of duodenal ulcer have become increasingly effective and current investigations give promise of making them even more so. At the present time it is recognized that medical treatment should be the primary form of therapy in virtually every case of duodenal ulcer.

SURGICAL INDICATIONS

Granting that medical treatment should be employed routinely in the management of duodenal ulcer, what are the indications for surgical treatment? In our experience[7] at the Mayo Clinic surgical intervention is necessary in only about 10 to 12 per cent of cases in which the diagnosis of duodenal ulcer is made. The complicating features which may render surgical treatment advisable are generally recognized to be perforation, obstruction, hemorrhage, failure of medical management and any question as to the benignity of the lesion.

All agree that acute perforation of a duodenal ulcer constitutes a surgical emergency which usually requires only simple closure of the perforation. The subacute perforating ulcer is one of pronounced activity causing varying degrees of penetration through the wall of the duodenum. In the advanced case the entire thickness of the wall of the duodenum has been eroded and the base of the crater consists of adjacent tissue, usually pancreas. When an ulcer of such pronounced activity is present medical management often will be unsatisfactory.

Obstruction caused by duodenal ulcer may be either inflammatory or sclerotic in nature. The inflammatory type usually is seen during a subacute exacerbation of symptoms. Under proper medical management in a case of this type obstructive symptoms usually will disappear in a week or ten days. After several such episodes, however, it is doubtful whether medical measures will effect lasting relief. When a definite cicatricial type of obstructive lesion exists, the problem is at least

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† Division of Surgery, Mayo Clinic, Rochester, Minnesota.

partially mechanical in nature and surgical intervention becomes essential.

Hemorrhage may present itself either as active massive bleeding or as a history of recurrent bleeding without active bleeding when the patient is examined. Opinion differs as to the type of treatment advisable for acute massive bleeding. At present it is our practice to institute medical treatment in all cases in which massive bleeding occurs. If the patient is more than 45 years of age and medical treatment has been continued for 48 hours and there is evidence of continued or recurrent bleeding, immediate surgical intervention is advised. A history of recurrent hemorrhage, particularly if the hemorrhage comes with little warning or while the patient is following a fairly good medical regimen, makes surgical treatment seem advisable.

Failure of medical management to relieve symptoms of ulcer long has constituted an indication for surgical treatment. Care must be exercised, however, in determining just when failure of medical management has occurred. One should be satisfied that an adequate regimen has been followed.

Occasionally uncertainty will exist regarding the exact diagnosis in a case of suspected duodenal ulcer. This occurs most often when there is an obstructing lesion at the pylorus. One should remember that a small carcinoma in this region can closely simulate a benign ulcer. If uncertainty exists in this differential diagnosis operation should be advised.

Other factors which in a borderline type of case may influence one's opinion in favor of surgical treatment include excessive gastric acidity, long history, unfavorable social or economic status of the patient which virtually prevents satisfactory medical treatment and symptoms of such severity or persistence that a medical regimen is required which is incompatible with a normal life.

VAGOTOMY

Physiologic Aspects:

The excellent work of Dragstedt and his associates,[9-13,15,29] which has been published in a series of reports starting in 1943, has clarified and expanded knowledge of the neurophysiology of the human stomach. These physiologic observations pertaining to the vagus nerves have been substantiated by Moore, Grimson,[14,28] and their associates. In brief, earlier work on the physiology of the vagus nerves in the experimental animal[3,16,19,22,26,30] has been corroborated in some instances and further developed in other regards. Pavlov first demonstrated the importance of these fibers in the cephalic or psychic phase of gastric secretion. After complete section of all vagal fibers to the stomach this portion of gastric secretion is eliminated.

In contrast with certain opinions,[26,32] it has now been shown that the human stomach secretes constantly.[11,17,27] In the normal person, in the absence of stimulation caused by ingestion of food, the secretion is relatively small in amount and the value of free acid which it contains is low. In the patient who has a duodenal ulcer the reverse is true, the amount of secretion is large and the value for free acid is relatively high. For example, Dragstedt[11] found that the normal person secretes 250 to 400 cc. of gastric juice during the night. This secretion contains free hydrochloric acid ranging in amount from 0 to 20 clinical units. In contrast, a patient who has duodenal ulcer secretes during the night 600 to 2,500 cc. of gastric juice which contains free acid ranging in value from 40 to 110 clinical units. Calculated in terms of acid it is estimated that a patient who has duodenal ulcer secretes two to ten times as much hydrochloric acid as the normal person. Dragstedt[11] has observed further that this excessive nocturnal secretion found in the patient who has duodenal ulcer is reduced to normal after resection above the stomach of all vagal fibers. The clinical corollary is obvious when one considers the importance of gastric acids in the causation of duodenal ulcer.

It has been accepted for some time that stimulation of the vagus nerve produces gastric juice high in pepsin as well as in hydrochloric acid. Reduction of pepsin may be almost as important as reduction of acid when one considers the strong proteolytic properties of this enzyme in the presence of an acid mixture. In fact, probably one should always speak of the "acid-pepsin factor" in reference to the production of duodenal ulcer rather than merely the "acid factor," which has come to be the term commonly used. The "neurogenic factor" long has been recognized clinically as one of importance in cases of duodenal ulcer. It is interesting to speculate on the possible elimination of this factor by vagotomy.

Histamine produces the same response after vagotomy as it does when the vagus nerves are intact. However, after the administration of a test meal, if the vagi have been severed, gastric acidity does not usually rise to the level noted prior to vagotomy because of the abolition of the psychic phase of gastric secretion. Another interesting observation[1] is the absence of any emotional effect on the appearance of the gastric mucosa after vagotomy. The full significance of this observation awaits further study. The failure of hypoglycemia to produce stimulation of gastric secretion after vagotomy forms the basis of the insulin test described by Hollander.[18]

In addition to the effect on gastric secretion exerted by the vagus nerves, a pronounced effect on gastric motility is evident. Although both motor and inhibitory effects may be demonstrated by proper stimulation of the vagus, the effect of this nerve on the gastric musculature is primarily motor. Thus, after complete vagotomy motility of the stomach is decreased. This may be observed both experimentally and clinically. Abolition of an inhibitory influence on the pylorus may be a factor in the prolonged time required for the stomach

to empty which is evident after section of the vagi. Gastric hypomotility has been responsible for certain undesirable clinical symptoms following vagotomy.

It is of definite interest that Moore and associates have noted some return to normal of gastric motility and gastric secretion, especially nocturnal secretion, one year after vagotomy. Response to the insulin test has remained negative, however, a fact which suggests that vagal continuity has not been restored. Comparable observations have been made on experimental animals.[30]

Technical Aspects:

The vagi may be severed above the diaphragm through a thoracic approach or below the diaphragm through an abdominal approach or a combination of these two approaches may be used by incising the diaphragm either from above or below and dissecting the vagal fibers for a distance on the other side. Opinions[4,23] differ regarding the approach which affords the best opportunity for complete section of all vagal fibers. The abdominal approach possesses the obvious advantage that an opportunity is presented for exploration of the abdomen and direct inspection of the lesion. Furthermore, any additional procedure on the stomach which appears advisable can be performed at the same time. Generally, in my experience, one can be more certain of locating all vagal fibers if the thoracic approach rather than the abdominal one is used.

If the thoracic approach is utilized, resection of the left eighth rib affords adequate exposure. Mobilization and isolation of the esophagus, after the pulmonary ligament has been severed and the left lung has been retracted upward, permits careful dissection of the vagal trunks just above the diaphragm. These usually occur in two main bundles with several intercommunicating branches but the anatomic arrangement of these nerves at this level is variable and numerous branches may be present in some cases. Two or three centimeters of each nerve should be resected.

If the abdominal approach is employed a midline incision, or preferably one to the left of the midline, is desirable. The esophagus is isolated by blunt dissection and a gauze tape is slipped around it to aid exposure of the nerves by caudal traction and rotation of the esophagus. The peritoneum overlying the esophagus is severed transversely to facilitate mobilization of the underlying structures. Generally it is helpful to sever the triangular ligament which attaches the left lobe of the liver to the diaphragm and retract the liver to the right to aid visualization and mobilization of the esophagus. The nerves are located by palpation and also by direct vision. Again, a generous portion of each nerve should be resected.

Clinical Results:

Accurate evaluation of the effectiveness of vagotomy in the treatment of ulcer requires first that a uniform type of case be considered, second that the vagotomy be complete and third that no associated surgical procedure be performed. Three methods are used currently to determine whether vagotomy has been complete: the insulin test of Hollander, the response to sham feeding and the amount of gastric secretion produced during the night. To obtain accurate information the postoperative results of a given test should be compared with the preoperative findings. Probably no one of these tests affords entirely reliable evidence regarding the completeness of a given operation; however, they are the best tests available at this time. The development of marked gastric hypomotility after vagotomy, as evidenced by gastric retention in the absence of any demonstrable organic obstruction at the outlet of the stomach, probably affords the most reliable evidence that all vagal fibers to the stomach have been severed. Kymographic tracings made from a balloon in the stomach reveal objective evidence of decreased gastric motility after complete vagotomy but such observations do not afford a wholly satisfactory clinical test. The vagus nerve does not transmit sensory fibers from the stomach. Relief of pain caused by ulcer after section of the vagi probably is explained on the basis of decrease of gastric acidity and motility.

Although vagotomy was employed many years ago,[2,20,21] in the treatment of a limited number of patients who had duodenal ulcer, for various reasons significant interpretations of the clinical results in these cases were not established. Since the reintroduction of vagotomy by Dragstedt, insufficient time has elapsed for evaluation of ultimate results. Early results have been reported by various authors but, unfortunately, these are not easy to evaluate. In some instances, opinions of the same authors have varied from one year to the next. Certain reports have appeared in which evidence is lacking regarding the completeness of the operation. In other reports cases have been included in which vagotomy was combined with gastro-enterostomy. As mentioned previously, it is impossible to evaluate the effectiveness of vagotomy per se, at least until many years have elapsed, if it is combined with gastro-enterostomy. In certain other reports cases of jejunal or gastric ulcer have been included with cases of duodenal ulcer, a procedure which makes evaluation of any one group difficult.

Dragstedt and his associates[15] recently reported 170 cases in which vagotomy had been performed during the past four years. In 61 of these cases the thoracic approach was employed. In 109 cases the abdominal route was used and in 71 cases gastroenterostomy was performed simultaneously. In five of the group it was necessary to perform gastroenterostomy after the vagus nerves had been severed, because of gastric retention. In the entire group of 170 cases, duodenal ulcer was present in 147, gastrojejunal ulcer in 15 and gastric ulcer in eight. Postoperative secretion studies showed evi-

dence of incomplete vagotomy in 14 cases and in five of these recurrent ulceration has already occurred. There was one postoperative death in the 170 cases. Clinical results for duodenal ulcer are considered excellent.

Moore has reported 74 cases in which transthoracic vagotomy alone was used. Of this group vagotomy was performed for duodenal ulcer in 57 cases, for jejunal ulcer in 16 cases and for gastric ulcer in one case. Moore considered that the early results were good in 75 per cent of cases, fair in 18 per cent and poor in 7 per cent. In two cases subsequent gastro-enterostomy was necessary. Diarrhea occurred postoperatively in 62 per cent of cases. Emptying disorders, such as postprandial fullness and belching, were evident in 69 per cent of cases. In most instances these side effects were neither severe nor prolonged. Walters and his associates have reported 83 cases of vagotomy with variable results. In most of these cases some additional surgical procedure was performed on the stomach.

Grimson reported 57 cases in which vagotomy alone was performed. There was one postoperative death in the group. In five cases subsequent gastro-enterostomy was necessary. The operation was done for duodenal ulcer in 32 cases. In approximately 70 per cent of cases there was postoperative evidence of disturbance of motility but in only 30 per cent did these symptoms persist as evaluated in a follow-up period of six months to three years. Grimson concluded that vagotomy alone should not be used as a standard operation for duodenal ulcer. Colp reported 20 cases of thoracic vagotomy for duodenal ulcer, in four of which subsequent abdominal operation was necessary because of gastric retention.

Obviously, clinical evaluation of vagotomy for duodenal ulcer is in the formulative stage at the present time and only the greatest enthusiasts or skeptics are willing to express definite opinions on the subject. It would seem wise to retain an open mind and permit more time to pass before reaching final judgment. In the meantime it is my personal opinion that the majority of us should await late results in a few well-controlled series of cases that are already under study rather than now abandon time-tested procedures of considerable satisfaction and efficacy. If one accepts this viewpoint, at the present time vagotomy is recommended only in the exceptional case of duodenal ulcer for which surgical treatment is undertaken. In a typical case the patient would be a man 20 years of age, with a large neurogenic factor, excessive gastric acids and severe symptoms which are uncontrollable by the most careful medical management. In the absence of any gastric obstruction as evidenced clinically, by roentgenologic examination or motor test meal, thoracic vagotomy might be suggested in such a case. In the presence of obstruction, abdominal vagotomy associated with gastro-enterostomy or possibly gastric resection might be recommended. I am inclined to believe that currently the most clear-cut indication for vagotomy is in a case of jejunal ulcer following gastric resection. For duodenal ulcer, at the present time, gastric resection remains, in my opinion, the treatment of choice in most cases although it is true that in many regards this operation is far from ideal. When confronted with an exceptional type of case in which there is little of proved efficacy to offer, vagotomy may be a proper procedure, either alone or in association with some other procedure, according to the findings in the individual case.

GASTRIC RESECTION

Various types of gastric resection have been suggested and performed for duodenal ulcer. Ultimate results vary, depending on the type of resection performed and the amount of stomach removed. Cure of duodenal ulcer by gastric resection is dependent primarily on reduction of gastric acidity. The incidence of recurrent ulceration after properly performed gastric resection for duodenal ulcer probably is less than 5 per cent. If free acid is present in the gastric secretion after gastric resection the chance of subsequent ulceration is increased. While it is difficult for various reasons to estimate accurately the exact percentage of the stomach removed at the time of operation it is necessary to remove two-thirds or four-fifths of the stomach to render free hydrochloric acid absent on subsequent analysis of gastric contents. The amount of stomach that needs to be removed to accomplish this purpose varies in different patients. Regardless of the type of anastomosis that is established, an adequate amount of stomach must be removed if subsequent ulceration is to be avoided in a high percentage of cases. Also, it has been demonstrated repeatedly that all of the mucosa of the pyloric antrum must be excised if satisfactory results are to be obtained. Granting these primary premises, what type of restoration of gastro-intestinal continuity is preferable after excision of the gastric segment of appropriate size?

Type of Resection:

I believe the ideal type of operation for duodenal ulcer, when feasible, is the Billroth I, preferably with the Schoemaker modification. In this procedure, after resection of the stomach a portion of the stomach on the side of the lesser curvature is closed and the remaining opening in the stomach is anastomosed to the end of the duodenum. The advantages of this procedure are as follows: normal gastro-intestinal continuity is maintained, fewer suture lines are necessary than if a gastrojejunal anastomosis were established, closure of the duodenal stump is obviated and the possibility of jejunal ulcer is avoided. Should subsequent ulceration occur in the duodenum, the patient's condition is virtually no worse than before resection was performed.

Unfortunately, the Billroth I operation cannot be performed satisfactorily in a high percentage of

cases of duodenal ulcer because fixation, inflammatory reaction and shortening of the duodenum render it unsuitable for anastomosis with the stomach. At other times it is impossible to remove an adequate amount of stomach and effect a gastroduodenal anastomosis without tension. Thus, the operation is suitable only in a selected group of cases. This fact should be stressed, as one's primary concern should be removal of an adequate amount of stomach and the establishment of a gastroduodenal anastomosis should be a secondary consideration. Thus, a good practice is to proceed with resection of the stomach at the desired level and determine only after this has been accomplished whether the end of the stomach and the duodenum should be united. If such an anastomosis would create tension on the suture line the duodenal stump should be closed and a gastrojejunal stoma should be established. In general, a thin person, whose costal margins form an acute angle and who has a low-lying stomach and a mobile duodenum which has not been greatly narrowed or otherwise altered by ulceration, represents the type in which a satisfactory Billroth I type of operation may be accomplished. In contrast, a thick-chested, obese person who has a small, high-lying, transversely placed stomach, seldom is a suitable subject for this type of procedure.

The next choice of resection for duodenal ulcer, in my opinion, is the posterior Hofmeister-Polya type of operation with a short proximal loop of jejunum. This operation is almost universally applicable except when an unusually short, thick transverse mesocolon is encountered or some anatomic abnormality or disease renders impracticable an anastomosis placed posteriorly to the transverse colon. In this operation a portion of the gastric stump on the side of the lesser curvature of the stomach is closed and a gastrojejunal stoma approximately 5 cm. in length is established. The dependent end of the stoma extends to the greater curvature. This type of anastomosis is preferred in contrast with the original Polya operation, in which the entire cut end of the stomach is anastomosed to the side of the jejunum, because it is followed less often by occurrence of the "dumping" syndrome.[8] Furthermore, if this syndrome does occur following a Hofmeister-Polya operation it is usually temporary, in contrast to the majority of cases in which it occurs after the Polya operation, in which it may last for years. While these symptoms are not frequent after the Polya operation, when they do occur they are most annoying to the patient. To my knowledge the Hofmeister modification is not followed by any undesirable sequelae which may not occur after the Polya operation.

The Polya type of resection has been a standard procedure, probably used more frequently than any other operation, since gastric resection became widely employed in this country for the treatment of duodenal ulcer some 15 years ago. Prior to its use for benign ulcer it has been employed more or less routinely by many surgeons in the treatment of gastric cancer. From a physiologic point of view it permits resection of the stomach adequate to effect the desired reduction of gastric acidity. Postoperative motor function is satisfactory in almost all cases, being or becoming unsatisfactory only when technical difficulties, anatomic variations or recurrent inflammatory lesions develop. In this type of operation the entire end of the gastric stump is anastomosed to the side of the jejunum so that a gastro-enteric stoma of generous size, depending on the size of the stomach, is established. Many surgeons still prefer this operation, as the one of choice for duodenal ulcer, and many eminently satisfactory results have followed its use. The posterior type of anastomosis is preferred.

Unpleasant sequelae such as the "dumping syndrome" were found to occur in 5 to 12 per cent of cases in one study. Although the actual cause of these symptoms is not established beyond doubt, the explanation most widely accepted currently is sudden dilation of the jejunum caused by rapid emptying of the stomach. The symptoms, which consist of postprandial weakness, sweating, nausea and cardiac palpitation, may be most difficult to relieve. Agents which tend to prolong emptying time of the stomach, such as fats, hydrochloric acid if there is achlorhydria, and occasionally ephedrine before meals, may be helpful. It is my practice to use the Polya operation if the stomach is small.

GASTRO-ENTEROSTOMY

Although gastro-enterostomy is an operation which has been used for many years in the treatment of duodenal ulcer and which has effected many favorable results, it is used infrequently today because of the relatively high incidence of jejunal ulcer which has followed its use. Gastric resection can be performed with a mortality rate comparable to that associated with gastro-enterostomy and with more favorable late results. The amount of gastric secretion and degree of gastric acidity are not reduced by gastro-enterostomy, the gastric contents merely being shunted from the duodenum into the jejunum. This change permits healing of the duodenal ulcer if the gastro-enteric stoma functions satisfactorily because under these circumstances the pH of the duodenal contents remains neutral or slightly alkaline. Although the duodenal ulcer heals, the possibility of an ulcer developing in the jejunum always is present. Motor function after gastro-enterostomy is entirely satisfactory in most cases.

Although, if the operating surgeon has had appreciable experience with gastric resection, gastro-enterostomy today seldom is a procedure of choice in the treatment of duodenal ulcer, it may be indicated occasionally. In a patient beyond middle age, in poor general condition, who has low gastric acids, who perhaps has had a long-standing sclerotic type of duodenal obstruction without an active ulcer and whose state of nutrition has become extremely depleted through a process of gradual starvation, a conservative operation such as gastro-enterostomy

may be advisable. Occasionally gastro-enterostomy may be employed as an operation of expediency if the technical difficulties of gastric resection are such as to render this procedure unreasonably hazardous. Under these circumstances the patient should remain on an ulcer type of regimen postoperatively if the greatest assurance against jejunal ulceration is to be afforded. Simultaneously abdominal vagotomy might also be advisable.

TECHNICAL CONSIDERATIONS OF GASTRIC RESECTION

Duodenal Stump:

Proper management of the duodenal stump has long been recognized as one of the more important considerations when gastric resection of the Polya type is performed. Probably because of the emphasis which has been placed on proper closure of the duodenum, leakage from this region now is an uncommon occurrence. Depending on the extent and location of the pathologic process in the duodenum, one of various methods of dealing with the duodenal stump may be found advantageous. The site at which the duodenum is severed, in relationship with the ulcer, always is a matter of concern to the surgeon. Preferably, the duodenum is sectioned distal to the ulcer, the latter is removed and the duodenum is closed distal to the ulcer. In some cases, this may not be possible, because of the location of the ulcer or marked shortening of the proximal portion of the duodenum, incident to a long-standing and recurring inflammatory reaction. Although the normal distance from the pylorus to the ampulla of Vater is 7 to 10 cm., in certain cases of duodenal ulcer this may be shortened to a length of only 2 or 3 cm. In my experience actual removal of the duodenal ulcer is unnecessary and it never is so important a consideration as to warrant reimplantation of the common duct into the duodenum for the sole purpose of removing the ulcer. Likewise it seldom is necessary to open the common duct merely to insert a T tube, for the sake of aiding in recognition of the anatomic relationships of the duct.

If the ulcer is placed deeply there may be an adequate amount of the duodenum between the ulcer and the pylorus to permit section of the duodenum immediately distal to the pylorus and closure of the stump proximal to the ulcer. Under these circumstances the ulcer subsequently is bathed in the neutral or alkaline duodenal juices, is completely removed from the digestive effect of gastric juice and will heal uniformly. Likewise, permitting the ulcer to remain in no way affects the possibility of subsequent jejunal ulceration. Frequently it will be found most convenient to sever the duodenum right at the site of the ulcer. This is particularly true in case one is dealing with a deeply penetrating ulcer of the posterior wall which has caused considerable reaction in the pancreas. The base of the crater need not be removed from the pancreas but the adjacent walls of the duodenum must be mobilized adequately to permit accurate closure.

A procedure which is not recommended is to sever the stomach proximal to the pylorus and permit some of the prepyloric mucosa to remain. The incidence of subsequent jejunal ulceration after this type of operation is relatively high. If the stomach is sectioned at this level the gastric mucosa may be excised down to the pylorus and the remaining muscular wall of the stomach closed by approximation or invagination. This, however, is not a procedure of choice, as it may be difficult to be certain that all of the remaining gastric mucosa is excised and closure of the gastric wall may not be as satisfactory as one would like.

Whether any special device or clamp is utilized in closing the duodenal stump is a matter of individual preference by the surgeon. Often the use of any clamp will be found impractical and direct suture of the "open" duodenum will be found most useful. One should routinely add to the safety of the duodenal closure by "rolling" the line of closure medially so that it is buried in the pancreas. This is accomplished by approximating the anterior wall of the duodenum to the nearby pancreas by means of a few interrupted stitches of silk. Adjacent parts of the duodenohepatic and duodenocolic structures may be used to protect the superior and inferior ends of the suture line in the duodenum if one desires.

Length of Proximal Jejunal Loop:

Most surgeons now are in agreement that, when a gastrojejunal anastomosis is made, the length of the jejunal loop from the ligament of Treitz to the stomach should be short, not longer perhaps than 8 to 10 cm. Experimental evidence substantiates the statement that the incidence of jejunal ulcer is higher if a long loop is used than if one of short length is employed.

Anterior or Posterior Anastomosis:

Whether a gastrojejunal anastomosis should be placed anterior or posterior to the transverse colon in performing a polya type of gastric resection has long been a subject of discussion. The majority of surgeons experienced in this field prefer the posterior anastomosis although some still employ the anterior type. I believe the strongest argument against the latter is the fact that it requires a relatively long proximal loop of jejunum with the undesirable sequelae which this might produce. Motor function seems to be equally satisfactory after either type; however, it is my impression that the posterior anastomosis is somewhat superior in this regard to the anterior. The anterior anastomosis is easier to establish than the posterior one and occasionally may be necessary if the transverse mesocolon is unusually short and thick or an exceptionally high resection has been performed.

Postoperative Retention:

Many viewpoints have been expressed regarding the occurrence and cause of gastric retention after either gastro-enterostomy or gastric resection. In

my opinion it is determined in the majority of cases at the time of operation whether subsequent gastric retention will or will not occur. It is true that in a small number of cases edema at the gastro-enteric stoma, perhaps augmented by hypoproteinemia, may be a factor in the occurrence of retention; however, I believe that this is the exception rather than the rule.[5] Likewise in the exceptional case angulation, inflammatory reaction or other change may take place in the distal loop of jejunum and give rise to a mechanical obstruction. In most cases, however, proper attention to certain technical aspects of the operation will avoid postoperative gastric retention.

The most important points to keep in mind in this regard are: establishment of an anastomosis so that the distal loop of jejunum is attached to the greater curvature of the stomach; proper location of the gastro-enteric stoma in the stomach; anchoring of the transverse mesocolon on the stomach at a level well removed from the gastrojejunal anastomosis; avoidance of too large an enfolded cuff of stomach and jejunum in establishing the gastro-enteric stoma, especially in the region where the distal loop of jejunum leaves the stomach; and replacement of the jejunal loops in their normal location on the left side of the abdomen at the conclusion of the operation. It is advisable to have the gastro-enteric stoma extend down to the greater curvature of the stomach and to attach the distal loop of jejunum to the stomach at this point. Likewise in arranging the viscera at the conclusion of the operation this distal loop of jejunum should be placed in the left side of the abdomen, where it normally lies. If a posterior type of anastomosis is established the gastro-enteric stoma should be brought well down below the transverse mesocolon and the mesocolon should be sutured to the stomach at a distance of at least 3 cm. from the anastomosis. Under these circumstances if the stomach retracts upward, a loop of jejunum is less likely to be drawn above the mesocolon and angulated than if the mesocolon had been sutured to the stomach close to the gastro-enteric stoma.

The diameter of the distal loop of jejunum at the point where it leaves the stomach obviously determines the caliber of the lumen through which food must pass when it leaves the stomach. If there is too much inversion of the stomach and jejunum at this level, when the anastomosis is established, it is apparent that there may be interference with proper emptying of the stomach. This interference usually is most marked during the early postoperative period while edema is present around the suture line and before a certain amount of the inverted cuff of tissue sloughs, during the normal process of ultimate healing.

SUMMARY

Only approximately 10 to 12 per cent of patients who have duodenal ulcer require surgical treatment. Obstruction, hemorrhage, perforation, failure of medical management or uncertainty of diagnosis between a benign and a malignant lesion are indications for surgical treatment.

Elimination of the neurogenic stimulation of gastric secretion and consequent lowering of gastric acidity by means of vagotomy has a beneficial effect on the patient who has duodenal ulcer. A number of favorable early results have been reported after this operation. At the present time, however, vagotomy is still in the phase of clinical trial. The difficulty of evaluating the clinical effect of vagotomy, per se, the possibility of incomplete section of all vagal fibers even in the hands of an experienced surgeon, undesirable effects of vagotomy on gastric motor function and uncertainty regarding the late results following vagotomy must all be considered in the current appraisal of this procedure.

Gastric resection in the meantime should remain a routine procedure for most surgeons in the treatment of duodenal ulcer. The posterior Hofmeister-Polya operation and in selected cases the Billroth I procedure are the preferred types of resection in most cases. Resection of the stomach adequate to effect achlorhydria and attention to certain technical details are essential for the best postoperative results.

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The Use and Abuse of Desiccated Thyroid*

E. Kost Shelton,* M.D., *Los Angeles*

WHILE desiccated thyroid is the oldest and perhaps the most specific therapeutic agent employed in clinical endocrinology, there is still considerable misunderstanding regarding the indications for its use, the dose to be employed, and its untoward manifestations.

Because of its specificity in frank hypothyroidism, the results obtained from the administration of desiccated thyroid may be considered, within definite limits, as a valuable diagnostic criterion. This statement is qualified because of the large number of physiological and psychological variants to be considered before a definite diagnosis can be made in the obscure or borderline case. Let us consider the physiological problems first.

For many years observers interested in metabolic disorders have known that the level of oxygen consumption — as indicated by a so-called basal metabolic rate—is not a true, or perhaps I should say, not an infallible measure of thyroid function. It is also known that some individuals are refractory to moderate doses of thyroid and that not infrequently their basal metabolic rates fall to levels lower than those encountered before thyroid ingestion. This phenomenon was further elucidated by Farquharson and Squires.[1] They studied patients with normal or moderately depressed basal metabolic rates, who had normal cholesterol values and no clinical evidence of hypothyroidism. Some of the subjects were under treatment for obesity; the others were the ordinary mill run of patients with vague symptom complexes, rarely found to be on a metabolic basis.

The authors noted that when thyroid was administered in relatively small doses, the basal metabolic rates were promptly increased, but after two or three months they usually fell to, or close to, the initial level. Continued administration of larger doses (sufficient to raise the basal metabolic rates of myxedematous patients to normal levels), produced another rise in the basal metabolic rate, followed by a gradual decrease (Fig. 1). With still larger doses, the rate rose, and remained at an elevated level. When the excessive dose of thyroid was withdrawn after prolonged administration, the basal metabolic rate fell rapidly to a point below the patient's initial level. At the same time the patient complained of mild weakness, lassitude and fatigue, the pulse became slow, and there were other indications of deficient thyroid activity. The above results were obtained whether the patients were losing or gaining weight during therapy. Riggs, Man, and Winkler have also shown that the blood iodine falls to myxedema levels shortly after discontinuing thyroid medication given to normal individuals, and does not return to normal for five or six weeks.[3] Our experiences have been much the same. (Fig. 2.)

This depression of thyroid function accounts for the fact that many physicians give larger and larger doses of thyroid to patients, erroneously diagnosed as hypothyroid, in order to raise the oxygen consumption to levels they consider normal. I have seen many young persons with basal metabolic rates ranging from —15 to —20 and lower, who have been taking from three to eight grains of standard brands of desiccated thyroid daily for a number of years simply because some physician had attempted to elevate the basal metabolic rate to —10 or above. In other words, the physician was treating the basal metabolic rate instead of the patient. As a matter of fact, these normal individuals were actually made hypothyroid by injudicious thyroid administration. When the dose of administered thyroid reaches a point where it overcomes the artificially created deficiency and speeds up general body metabolism to an abnormal degree, the physician frequently considers his treatment a success. If, however, the basal metabolic rate cannot be raised to —10 or thereabouts without producing some evidence of thyroid intoxication, he usually asks for help.

In contrast to this refractoriness, true hypothyroid patients are sensitive to ingested thyroid and the basal metabolic rate promptly rises following the administration of even small doses (one-half to one grain daily). Rarely more than two grains of thyroid are necessary to maintain the severe myxedema patient in normal metabolic balance and some such individuals keep in perfect health on much less, namely, from one-half to one and one-half grains daily. (Fig. 3.)

In addition to the above, the technical flaws incident to the arrival at a figure representing the supposed basal metabolic level are legion. It might be well to again mention the vagaries of the patient, the machine and the technician, not to speak of such apparently minor items as the cold bed, the noisy or stuffy room, and the fact that most individuals suffer from claustrophobia.

If, then, one cannot depend upon the figure or even the interpretation of the figure when it is correct, what place has the basal rate in the diagnosis of hypothyroidism? In the adult it is one of a triad of laboratory devices designed to either verify or refute one's clinical impressions of a given case. The other two are the blood organic iodine and the blood

* From the Shelton Clinic, 921 Westwood Boulevard, and the University of Southern California, Los Angeles, California.

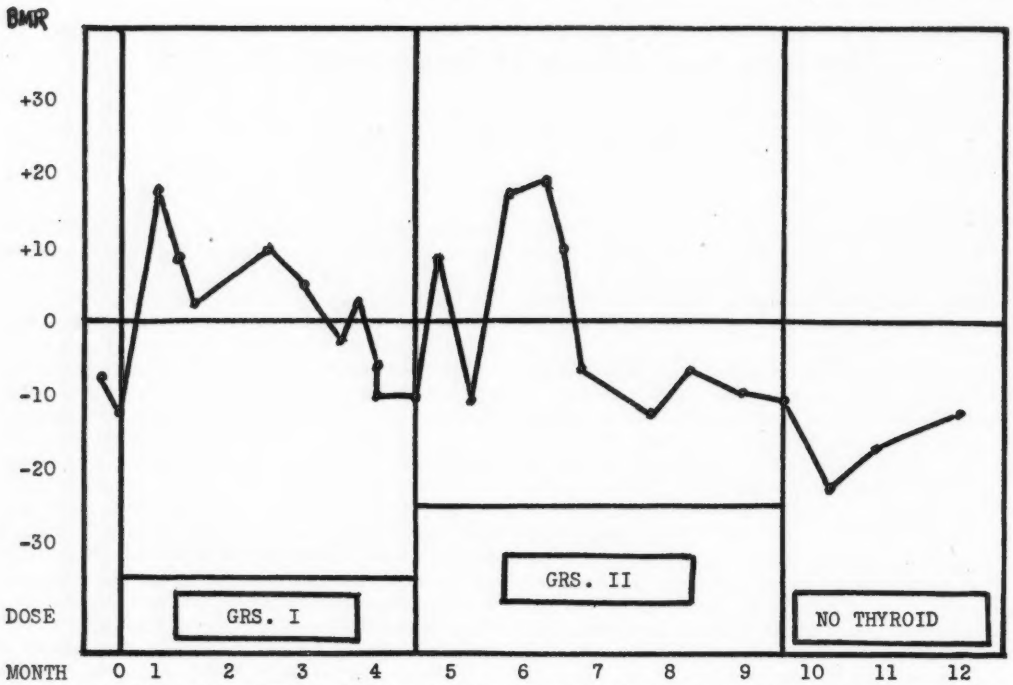

Figure 1.—Effect of Small Doses of Desiccated Thyroid on Basal Metabolic Rate of Normal (Non-Hypothyroid) Individual. (After Farquharson & Squires).

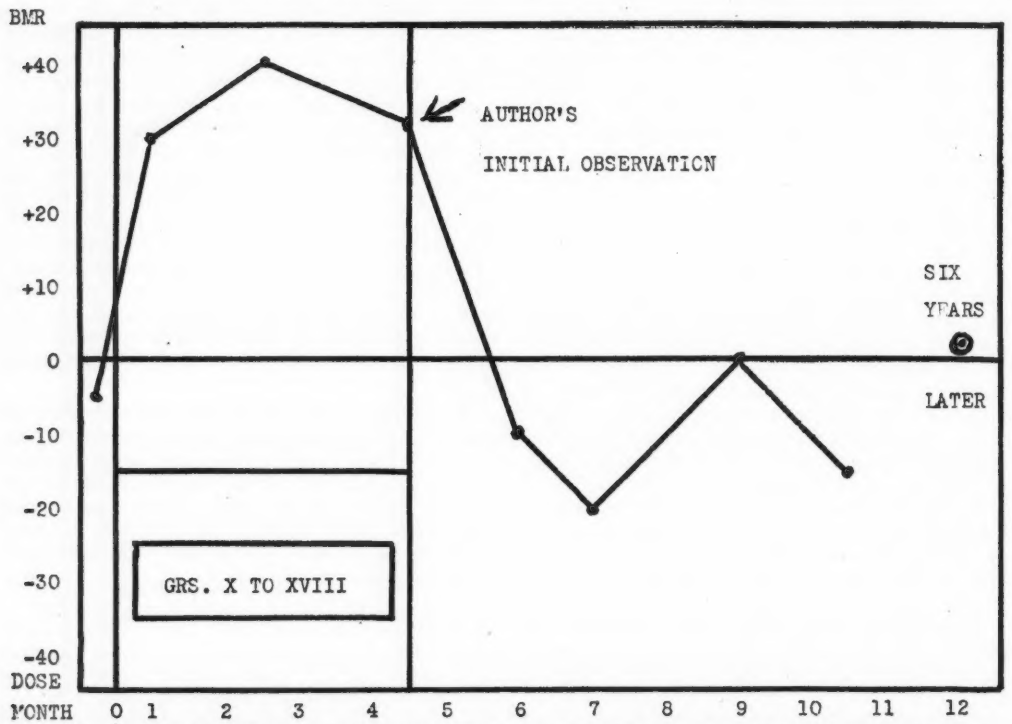

Figure 2.—Effect of Large Doses of Desiccated Thyroid on the Basal Metabolic Rate of a Normal (Non-Hypothyroid) Individual. (Author's Observation).

cholesterol. However, the iodine and cholesterol values, when considered alone, are subject to the same criticism, both as to the vagaries of the laboratory technique and the danger of dogmatic interpretation. In childhood the bone age and urinary excretion of creatin are also helpful diagnostic procedures.

While bone age continues to be the most objective evidence of the developmental status of the child, not all children with retarded bone age suffer from hypothyroidism.[4] Unfortunately, this writer has seen such a procedure endowed with as much diagnostic dogmatism as the basal metabolic rate. The same may be said of the urinary excretion of creatin in childhood. While all severely hypothyroid children excrete little or no creatin when not taking thyroid, not all children with poor urinary creatin excretion are hypothyroid. As in the case of the bone age, the urinary creatin excretion argues either for or against hypothyroidism in an otherwise carefully considered case.[5]

Even when the symptoms are vague and unorthodox, it is not difficult to arrive at a fairly prompt and accurate conclusion in the doubtful case of hypothyroidism, if a patient is not then or has not recently been taking thyroid. If the patient has taken thyroid recently (within three months) and he wonders if he really requires it—in other words, if he consults one for an opinion regarding his true metabolic status—it is necessary to discontinue the thyroid for at least three months so that the basal metabolic rate, iodine and cholesterol values can return to their non-treated or original levels. It is even better to study the patient while he is taking the thyroid and then check these values against those taken three months and even six months later. Many overzealous individuals who have been taking thyroid for years because of fatigue or depression or falling hair, or any one of a hundred complaints, could then be properly instructed to discontinue the thyroid because it is adding nothing to their welfare. However, it is sometimes difficult to get patients off of such medication, since they have created a temporary deficiency by overmedication. After the first shock of a-medication the normal individual gradually returns to his original metabolic status and feels much as he did when taking thyroid.

For example, A. L., age 19, consulted us December 12, 1945, because of nervousness and because she wished her thyroid medication adjusted. The patient had been taking thyroid for eight years, starting with grain 1 and going up to grains 4 daily. The basal metabolic rate was said to have been —30 originally (1937). As the thyroid dosage was increased, the basal metabolic rates rose slightly but were difficult to bring to normal. While the patient felt fairly well when taking grains 4 of thyroid daily, the basal metabolic rate would not go above —17.

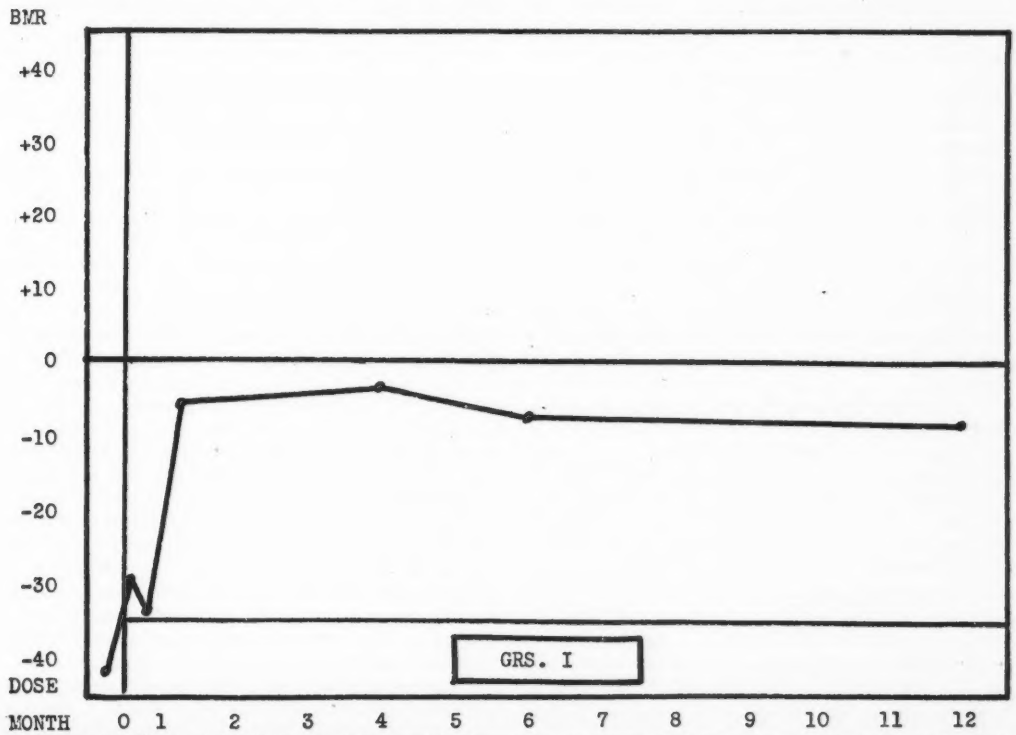

Figure 3.—Effect of Small Doses of Desiccated Thyroid on the Basal Metabolic Rate of Hypothyroid Patient (Myxedema). Modified After Farquharson & Squires.

Attempts to raise the basal metabolic rate above —17 with larger doses of thyroid always produced nervousness. Nine weeks before consulting us, the patient had been taken off of thyroid altogether by another physician. She became so cold and lethargic that she asked us to act in the capacity of a referee. To take thyroid or not to take it—that was the question. Our original observations were as follows: Basal metabolic rate —17, blood cholesterol 250 milligrams, blood organic iodine 3.2 micrograms. In spite of the low metabolic status, we advised her not to resume thyroid, but to come in again in three months for further study. At this time the basal metabolic rate was —10, blood cholesterol 140 milligrams, and blood organic iodine 5.7 micrograms—all normal findings. Still later, the basal metabolic rate was —4. The patient lost most of her nervousness and maintains a normal metabolic status without thyroid.

In contrast, the truly hypothyroid individual gradually regains his old spontaneous symptoms and may even develop myxedema. In the latter case the laboratory, if indicated at all, will soon verify the clinical impression and thyroid should be resumed.

The psychological factors to be considered are no less important, if not so confusing. What of the patient who complains of fatigue, but in whom no laboratory or clinical diagnosis of hypothyroidism can be made? Will thyroid alleviate the fatigue? It will not. Such patients have psychogenic or nutritional factors to account for their difficulties or possibly some hidden focus of infection. The same may be said of constipation, coldness, rough skin and so on ad infinitum. It is true that certain menstrual disorders, amenorrhea, oligomenorrhea, and menorrhagia are occasionally the result of thyroid deficiency and that some such afflicted individuals improve on thyroid. It seems a pity, however, that the nine sufferers whose etiology is not on a hypothyroid basis must be filtered out by injudicious thyroid administration in order to catch the one who really profits from such a regime. Such empiricism is excusable only when the patient is under careful scrutiny for a limited period. It is not unusual to see patients who have been taking thyroid for so long they have forgotten why it was originally administered.

In doubtful cases when one suspects hypothyroidism and does not have recourse to meticulous laboratory studies but must depend in a large measure upon his clinical judgment, I feel he should limit the therapeutic test period to no longer than two months. One should first take a careful history, outlining each and every one of the patient's complaints. If there are no immediate contraindications, such as coronary disease, a badly decompensated heart, active tuberculosis, etc., he may begin by giving the patient a half grain of a standard brand of desiccated thyroid once a day. Each week after this, increase the daily dose by a quarter of a grain until two grains are reached, and continue on this dosage for the balance of the two months. If, at the end of this period the patient is not enthusiastic about the results, he does not suffer from hypothyroidism, and the thyroid should be discontinued. If the majority of the symptoms have been alleviated, the patient is most likely hypothyroid and the minimum dose required (usually something between one and two grains a day) to keep him in good health, should be continued. While the patient should be observed every week during this trial period, one is justified in seeing him only at long intervals after the dose has once been established. One should take into account, of course, that in the case of the normal individual a minor state of hypothyroidism has been temporarily produced and the patient will need a few weeks to adjust to the let-down from thyroid withdrawal.

Other psychological factors of relatively minor importance might be mentioned. Since individuals who need thyroid, especially those with myxedema, are quite sensitive to ingested thyroid, the physician should be wary of the patient's reactions. I have seen patients with frank myxedema convince their physicians that they were so intolerant to thyroid that even one-tenth of a grain would produce severe nervous symptoms. In such a case it is best to give thyroid in a colored capsule and call it something else.

Some years ago I was called in consultation regarding such a patient. The woman, obviously suffering from myxedema, had convinced her local physician, as well as others in several large clinics throughout the country, that she was very intolerant of thyroid (which indeed she may have been temporarily). A pink capsule, ostensibly containing the thyrotropic hormone, but actually containing one-half grain of thyroid, completely rehabilitated the woman in a few months. The physician was later told of the deception and became quite angry.

Some patients complain that thyroid taken at night keeps them awake. I used to explain how such a reaction would be improbable. I now find it saves time and breath to tell them to take it in the morning. While we are on the subject I can see no reason why thyroid should be given oftener than once a day at the most convenient hour for the patient.

Thyroid is used consistently and erroneously in the treatment of obesity. In my judgment there is no such disorder as thyroid obesity; in fact more hypothyroid sufferers are thin than fat. If one has myxedema he will lose weight while taking thyroid until the myxedematous infiltration is metabolized and the by-products of his faulty protein metabolism are eliminated. After this point, thyroid will merely act as it does in the normal individual. Since we have pointed out that thyroid will depress the function of the gland, it could conceivably enhance rather than alleviate the deposition of fat. If one administers thyroid to the point where the metabolism is actually stimulated, increased appetite and nervousness often add to the patient's discomfort.

I have seen numerous obese individuals in whom physicians were trying to force a result by administering large doses of thyroid. One such patient was actually given eighteen grains of a very potent

desiccated thyroid daily for over a year. She was also placed on an eight-hundred calorie diet. If it had not been for the fact that she stole from fifteen-hundred to two thousand calories a day in addition to the diet, she would not have survived. While her basal metabolic rate rose to only +37 she became severely decalcified and lost several teeth through demineralization of the alveolar processes. The weight loss for that hectic year was eleven pounds. After thyroid was entirely withdrawn, the basal metabolic rate came back to around —12 in about six months, during which period she also lost forty pounds on a restricted diet. This is an outstanding example of the abuse the thyroid gland will tolerate and apparently still go back to a normal physiological status. (Fig. 2.)

It is ironical that while I was writing this paper a case report came to my attention in which an obese woman stole and ingested 100 grains of thyroid a day for over a year. She was ultimately discovered to be insane and died suddenly without benefit of autopsy. Goldfinger's [2] rather bizarre conclusion to this interesting case was that: "It is possible that too much conservatism in thyroid dosage has been used by the medical profession in the past. The factor of safety is large, and although exceeded in this case, it is suggested that a much higher dose (U.S.P.) may be used where the thyroid effect is desired. Further work upon the amount of thyroid necessary to increase the metabolic rate would seem to be in order to establish effective, but non-toxic dosage levels."

With such conclusions in the literature, it seems almost futile to preach conservatism.

Whether or not thyroid is indicated in the majority of individuals past middle age is problematical. Certainly the general metabolic processes, including thyroid function, are on the wane. This writer feels that much depends upon the arterial status and the level of the blood cholesterol. Blood cholesterol tends to rise in middle age and when no hepatic or renal disturbance can be demonstrated in one with elevated cholesterol levels, one is perhaps justified in administering small doses of thyroid over a long period without other verifying evidence of hypothyroidism.

While the injudicious use of large doses of thyroid in coronary disease and cardiac decompensation is to be deplored, one should not forget that some coronary disease is merely the end result of long-standing cholesteremia incident of hypothyroidism and some cardiac decompensation is due to a myxedematous infiltration of the myocardium. In either instance thyroid should be administered slowly, at the proper time, and in small doses. The shock of a too rapidly elevated metabolism is sometimes more than a weakened myocardium can tolerate. In such cases, the collaboration of an experienced cardiologist in treatment is paramount.

In childhood small doses of thyroid are anabolic while large doses are catabolic. When indicated nothing works in as spectacular a manner as thyroid in problems of growth and development. The most outstanding stimulation of growth I have obtained has been with doses ranging from one to two grains of thyroid daily. Larger doses have been advocated in cretinism, but it is my feeling that when two grains of thyroid will not rehabilitate a hypothyroid child, twice that much will have no better effect. If the dose is too high, calcium will be withdrawn rather than deposited, and the patient will remain on a negative mineral balance. Here again, if the patient is not truly hypothyroid, growth will not be stimulated and thyroid is more than useless.

Mixtures of thyroid and other medicaments are, in my judgment, bad medicine, unless it is first established that the patient really needs thyroid, and, second, what dose is required. Then and then only is the physician justified in adding another potent preparation such as benzedrine to a mixture designed to treat any disorder. Such preparations as we see for obesity containing thyroid, benzedrine, atropine, aloin, and what have you, are three steps back of the right direction, and should be left for our less scrupulous brothers, the irregular. When thyroid is combined with inert material such as whole ovary, testis, anterior pituitary, spleen, etc., your patient pays a fancy price for the leavings of the slaughter house and gets thyroid function and nothing else. When prescribing other hormones to a patient who also requires thyroid, give the most potent preparation available separately, so that you can evaluate each step of the treatment. All standard brands of desiccated thyroid are probably efficacious, but not necessarily grain for grain. It is best to employ one brand until one is thoroughly familiar with its potency and action. Then and then only are therapeutic comparisons of clinical value.

To sum up briefly then, thyroid is a specific drug in hypothyroidism. The administration of thyroid to normal individuals depresses thyroid function. A diagnosis of obscure hypothyroidism can be made both clinically and from the laboratory if a number of criteria are considered. Thyroid dosage in all cases, and in both children and adults, ranges from one-half to three grains a day. Small doses of thyroid are anabolic and large doses catabolic particularly but not exclusively in children. Small doses of thyroid probably postpone the aging process in middle-aged adults with moderately high cholesterol values. Thyroid should be administered alone until its full effect on a given individual is well established.

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Some Notes on the Rh and Hr Factors*

MARJORIE L. HUNT, M.P.H., and S. P. LUCIA, M.D., *San Francisco*

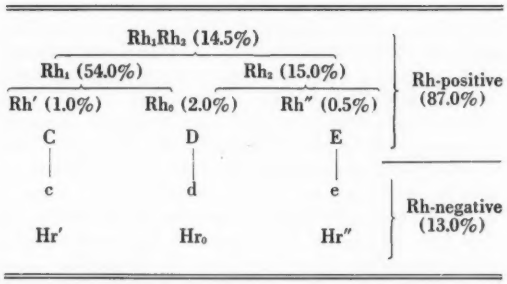
THE literature on the subject of the Rh-Hr factors and the antibodies they incite is not only complex, but in some instances it is confusing and contradictory. Often the line of demarcation between hypothesis and fact is not clearly drawn so that it becomes extremely difficult to determine the potential significance of the available information. The following discussion is an attempt to present the nomenclatures of Race and Wiener in a form easily comprehensible to a person not acquainted with the subject and at the same time to indicate the importance and usefulness of tests for Rh-Hr sensitization.

Rh and Hr Factors:

The Rh factor, present in the red blood corpuscles of at least 85 per cent of the random white population, is an inherited characteristic, and like the Landsteiner A-B-O agglutinogens, is a permanent consistuent of the red blood corpuscles of an individual. The Rh-positive population may be further subdivided into eight phenotypic groups by means of various combinations of the three Rh factor genes, called C, D, and E by Race, and Rh′, Rh_0 and Rh″ by Wiener. These factors are transmitted in the usual Mendelian manner and occur as "allelomorphic pairs."† The capital letters C, D, and E indicate dominant antigenic characteristics (Rh factors) whose "allelomorphs" (Hr factors) would be indicated by the small letters, c, d, and e (according to Race) and Hr′, Hr_0 and Hr″ (according to Wiener). In this manner the genetic possibilities of homozygous and heterozygous individuals may be determined.

The three Hr factors, c, d, and e, may also occur singly or in combination. A reciprocal relationship probably exists between Rh and Hr—for example, if gene C is absent, then gene c must be present, and likewise D—d and E—e. The factor Hr is apparently less antigenic and therefore usually of lesser clinical importance than the factor Rh.

The nomenclatures of Race‡ and of Wiener therefore may be represented schematically for genotypic§ incidence in the following manner:



Since genes occur in pairs, one set inherited from each parent, any combinations of $\frac{CDE}{cde}$ are possible as are shown in Chart I.

Interpretation of Reactions of Red Blood Corpuscles with Specific Antisera:

Since the red blood corpuscles of 85 per cent of the random white population contain the D (Rh_0) factor—Rh antiserum specific for D is most commonly used in testing for the presence of the Rh factor in blood specimens of unknown Rh characteristic. If the exact phenotypic character of the blood is desired, it is necessary also to use Rh antisera specific for C (Rh′) and E (Rh″) factors. Anti-C will agglutinate 70 per cent, and anti-E will agglutinate 30 per cent of the bloods of a random white population.

Anti-C sera will react with all red blood corpuscles containing C factor. Likewise anti-D or anti-E will react with all corpuscles containing D or E factors, respectively.

Anti-c sera will react with all red blood corpuscles containing c factor. Likewise anti-d or anti-e will agglutinate all cells containing d or e factors, respectively.

Hr sera are sometimes used to determine homozygosity of a husband; for example, if the husband is type Rh′ (Cde) it may be useful to know whether he is homozygous or heterozygous for the C factor, that is $\frac{Cde}{Cde}$ or $\frac{Cde}{cde}$. If he is homozygous his red blood corpuscles will *not* be agglutinated by anti-c (Hr′) serum since he does not contain the c factor.

Rh-Antibodies:

An individual whose red blood corpuscles lack a specific Rh factor may become sensitized when exposed to such a factor during pregnancy or following blood transfusions. An Rh negative individual may

* From the Blood Grouping Laboratory, Subdivision of Preventive Medicine, Division of Medicine, University of California Medical School, San Francisco.

† This term is used with reservations. For a pertinent discussion of the subject consult references 1 and 5.

‡ Race considers that the factors C—c, D—d, and E—e occur together within the red blood corpuscle and the presence of any one or more of the three dominant factors would therefore determine the phenotypic characteristic of Rh-positive individuals; the absence of all three dominant factors would indicate the Rh-negative individual.

§ Rh′, Rh_0, Rh″, Rh_1, and Rh_2 include the incidence of the pure phenotypic as well as the genotypic combinations.

CHART 1.—*Schema Showing Some of the Possible Rh Genotypes Which May Occur for Each of the Eight Primary Phenotypes**

(Data below the dotted line indicate uncommon occurrences)

Phenotypes	GENOTYPES		
	Complete homozygosity	Partial homozygosity	Complete heterozygosity
1) cde rh	$\frac{cde}{cde}$ (Rh′Rh′)		
2) Cde Rh′	$\frac{Cde}{Cde}$ (Rh′Rh′)		$\frac{Cde}{cde}$ (Rh′rh)
3) cDe Rh_0	$\frac{cDe}{cDe}$ (Rh_0Rh_0)		$\frac{cDe}{cde}$ (Rh_0rh)
4) cdE Rh″	$\frac{cdE}{cdE}$ (Rh″Rh″)		$\frac{cdE}{cde}$ (Rh″rh)
5) CDe Rh_1	$\frac{CDe}{CDe}$ (Rh_1Rh_1)	$\frac{CDe}{Cde}$ (Rh_1Rh′); $\frac{CDe}{cDe}$ (Rh_1Rh_0)	$\frac{CDe}{cde}$ (Rh_1rh)
6) cDE Rh_2	$\frac{cDE}{cDE}$ (Rh_2Rh_2)	$\frac{cDE}{cDe}$ (Rh_2Rh_0); $\frac{cDE}{cdE}$ (Rh_2Rh″)	$\frac{cDE}{cde}$ (Rh_2rh)
7) CdE $\underline{Rh_y}$	$\frac{CdE}{CdE}$ (Rh_yRh_y)	$\frac{CdE}{Cde}$ (Rh_yRh′); $\frac{CdE}{cdE}$ (Rh_yRh″)	$\frac{CdE}{cde}$ (Rh_yrh)
8) CDE $\underline{Rh_z}$	$\frac{CDE}{CDE}$ (Rh_zRh_z)	$\frac{CDE}{Cde}$ (Rh_zRh′); $\frac{CDE}{CDe}$ (Rh_zRh_1) $\frac{CDE}{cDe}$ (Rh_zRh_0); $\frac{CDE}{CdE}$ (Rh_zRh_y) $\frac{CDE}{cdE}$ (Rh_zRh″); $\frac{CDE}{cDE}$ (Rh_zRh_2)	$\frac{CDE}{cde}$ (Rh_zrh)

* This chart may be enlarged to include the genotypic formulas for any possible combinations of phenotypes. (The genotypes Rh′Rh″ ($\frac{Cde}{cdE}$) incidence 0.01% and Rh_1Rh_2 ($\frac{CDe}{cDE}$) incidence 14.5% are not included in this chart because they are composed of mixtures of phenotypes.)

therefore develop sensitization to any or all of the three factors (C, D, or E) depending on the phenotype of the immunizing cells and the biologic conditions which determine the immunization peculiarities of the individual. It is also possible for an Rh positive individual, for example one of phenotype Rh_0 (cDe) when exposed to corpuscles containing either the C or E factors (found in bloods of types Rh′, Rh_1, Rh″ or Rh_2) to become specifically sensitized to them. Therefore the exact phenotypic identification of the corpuscles is necessary in order to: explain cases of repeated transfusion reactions; explain cases of recurrent births of erythroblastotic infants in Rh-positive women; and account for any other Rh immunologic phenomenon which might not be explained by the usual routine Rh tests.

Individuals sensitized to the Rh factor by transfusion or pregnancy may demonstrate either or both of two types of Rh-antibodies, designated "agglutinating antibodies" and "blocking antibodies." Agglutinating antibodies combine with Rh-positive red blood corpuscles and agglutinate them; blocking antibodies also combine with Rh-positive red blood corpuscles but apparently do not agglutinate them.

The Rh antibodies are specific for the phenotype of the antigenic stimulus. Specific agglutinating antibodies have been found for all of the Rh and most of the Hr factors. A similar specificity exists in the case of the blocking antibodies, however, the most commonly reported blocking antibodies are those specific for the D (Rh_0) factor.

The significance of Rh-antibodies in the sera of pregnant women is still debatable, however a few *tentative* statements may be made:

1. The presence of any Rh-antibodies, either agglutinating or blocking, indicates sensitization of the host with Rh-positive red blood corpuscles either from a blood transfusion or a current or previous pregnancy.

2. If antibodies are found during the first few months of pregnancy and increase in amount as the pregnancy progresses, they may indicate: (a) An anamnestic rise of antibodies initially formed in the past and bearing no relation to the Rh characteristic

of the fetus *in utero*. In such an instance, the infant would be unaffected. (b) An Rh-positive fetus producing specific sensitization of the mother. In such an instance, the infant might be afflicted with hemolytic disease of the newborn.

3. If antibodies occur only within the last few weeks of pregnancy they may indicate initial sensitization in a mother not previously exposed to the Rh factor. In such an instance the infant might show mild symptoms of hemolytic disease of the newborn or be clinically normal.

In regard to the prediction of hemolytic disease of the newborn it may be stated that occasionally hemolytic disease of the newborn may occur in offspring of women who do not demonstrate any laboratory evidence of Rh sensitization. This occurs in roughly 10 per cent of the instances of the disease and is due to the A-B-O and Hr sensitization and other mechanisms. On the other hand, a clinically normal Rh positive child may be born to an Rh negative mother who shows abundant evidence of current Rh sensitization.

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Excretory Cystograms After Voiding

JAMES R. DILLON,* M.D., *San Francisco*

MANY pathological conditions of the upper urinary tract and bladder can be diagnosed and differentiated by excretory urography, not only from morphological deviation, but particularly by a study of the peristaltic action of the calyces, kidney pelves and ureters and the emptying power of the kidney and bladder.

In order to get the best results it is necessary: (1) to prepare the patient by dehydrating sufficiently to get a better concentration of the opaque solution in the urine, and (2) to clear the bowel of fecal material and gas. The most uniform results have been obtained by giving the patient instructions noted in Table 1.

TABLE 1.—*Instructions for Preparation for Excretory Urography*

1. Regular dinner the evening before the date set for the x-ray study.
2. No fluids and no food until after the x-rays are finished the next morning.
3. Two to four A. B. S. & C. Pills (Aloin, Belladonna, Strychnine and Cascara) at 9 p. m. the evening before, the number of pills depending on the patient's bowel activity.
4. If necessary, an enema one hour before the patient goes to the x-ray laboratory. No abdominal or pelvic binder or pressure bag should be used which might interfere with urinary peristalsis.

The next important step is that the proper technique be followed by the x-ray technician. The minimum study is indicated in Table 2.

TABLE 2.—*Technique for Making Adequate Studies in Excretory Urography*

Films of the urinary tract to be taken as follows:

1. Before the intravenous injection of the opaque solution.
2. Three to five minutes after the intravenous injection.
3. Fifteen minutes after injection.
4. Twenty-five minutes after injection.
5. In standing position (immediately after film 4). It should be taken after a few deep breaths while standing.
6. After voiding (a film taken through bladder region). Instruct the patient to empty the bladder completely.

All exposures except the last one on the list should be on 14 x 17 films for study of the entire urinary tract, including the bladder. The last exposure listed (6) through the bony pelvis after voiding, for the bladder region, should be on an 8 x 10 film.

The foregoing serves as an excellent routine technique for x-ray technicians to follow, but for a more accurate study the roentgenologist should study the first two or three urograms and note the rapidity of concentration of the opaque solution in the urinary tract, particularly the increasing density of it in the bladder. Then he can either lengthen or shorten the intervals for the suggested 15 and 25-minute films. In general the techniques noted in Tables 1 and 2 should be followed, but if concentration is slow in one or both kidney pelves, films should be made over longer periods such as an hour or two. Also, for greater accuracy, stereoscopic films should be made of Numbers 1, 3 or 4 (Table 2), according to the concentration of the opaque solution, and of Number 6.

There are thousands of excretory urograms taken by improper and insufficient technique, leading to wasting of films and failure to make an accurate diagnosis of disease. Since this report stresses particularly study of the cystogram taken after voiding, the cases presented here have been chosen because in them the most valuable diagnostic clue was given by that cystogram.

* * *

GROUP 1. Lower urinary tract obstruction.

Figures 1 and 2. Contracted bladder neck evidenced by a collection of opaque urine in the retrotrigonal pouch behind the hypertrophied interureteric ridge and also in the anterior pouch of the vertex of the bladder. The author considers this sign to be the one most valuable in diagnosis and the one most frequently seen. It always indicates urethral obstruction,

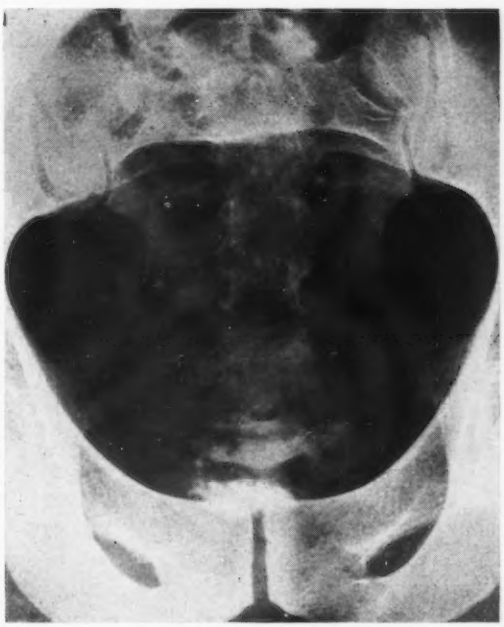


Figure 1

* From the Division of Urology, Stanford University Medical School, San Francisco.

particularly that of a fibrous contracted bladder neck in both sexes. In the male it also indicates median bar or early hypertrophy of the prostate, particularly in young adults and middle aged men. I think roentgenologists should become acquainted with this sign and include it in their reports, as it is often indicative of the cause of vague complaints of illness and gastrointestinal disturbances, without particular urinary tract symptoms at the time.

Figure 3. Contracted bladder neck with more residual urine and a chronic colon bacilluria which did not clear up under extensive chemotherapy until the base of the bladder neck had been grooved and followed by a few Kollman dilatations of the posterior urethra.

Figure 4. Stricture of the membraneous urethra evidenced by residual urine in the bladder, too much to show the above mentioned signs.

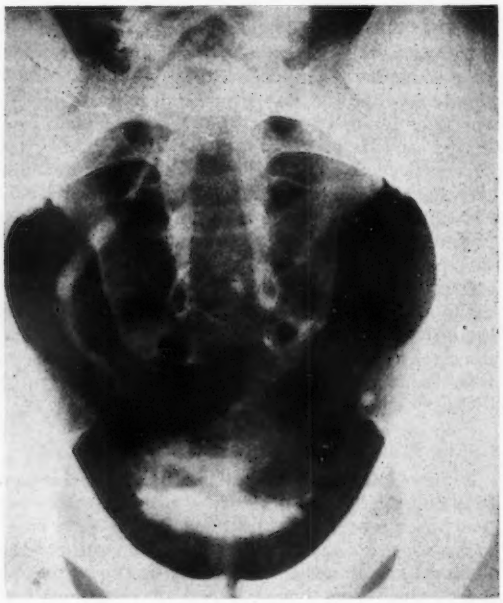


Figure 2

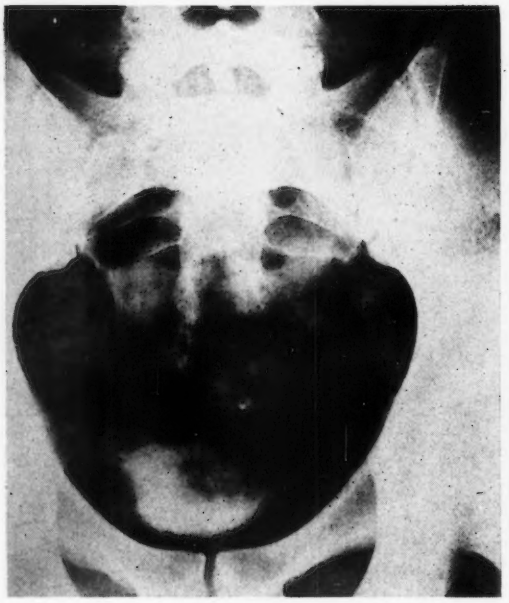


Figure 3

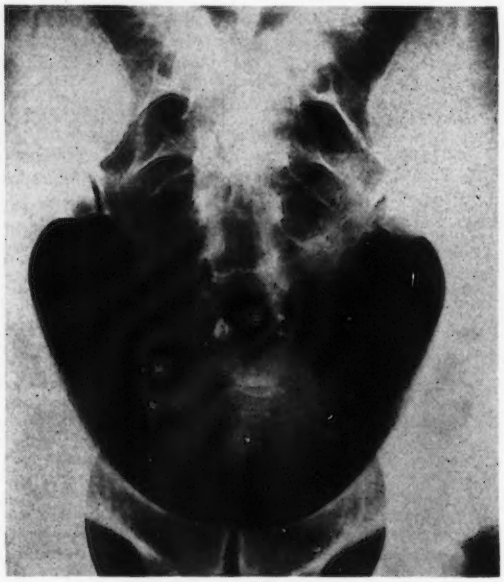


Figure 4

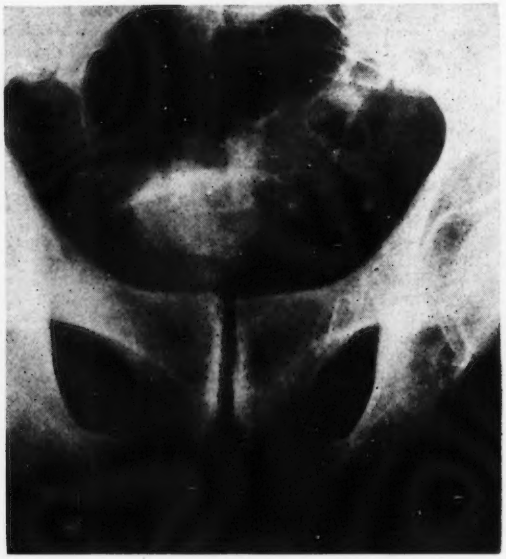


Figure 5

GROUP 2. Hypertrophied prostate, showing characteristic shadow (where there is not a great deal of residual urine) of a rounded mass causing a filling defect in the floor of the bladder in the region of the prostate. The following cases were less characteristic:

Figure 5. Residual urine was absent, but the ureter is being pushed upward and backward and this is evidence of a mass in the region of the prostate or floor of the bladder.

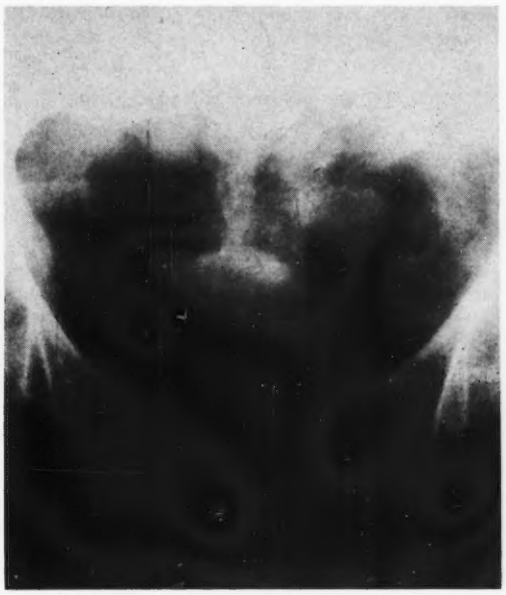


Figure 6

Figure 6. The preliminary films showed several stones 1 cm. or so in diameter in the bladder, but the excretory cystogram showed a tremendously hypertrophied bladder wall, with a small diverticulum. The bladder emptied completely although there was evidence of a tremendously hypertrophied prostate by the displacement of the ureter upward and backward. At operation 50 gm. of prostatic tissue was removed transurethrally, after which 12 stones were crushed and washed out.

Figure 7. Evidence of a large residual of urine and suggestion of a large prostate, which had preoperatively been diagnosed as malignant. At operation a primary malignancy of the bladder was found, with invasion of the prostate and infiltration around the seminal vesicles.

* * *

GROUP 3. Women with residual urine.

The normal nulliparous female bladder empties completely, though occasionally it may show just a few drops of residual urine with no characteristic outline in the region of the bladder neck. If a tendency to contracture of the bladder neck exists, it results in a cystogram similar to that noted in Figure 1.

Figure 8. A small amount of irregularly distributed residual urine, indicative of early trabeculation and bladder irritability — in this case due to polyps around the bladder neck.

Figure 9. A small amount of residual urine with a tremendously hypertrophied bladder wall. The patient was a 26-year-old nun with a long history of urinary frequency, incontinence, and pain with a

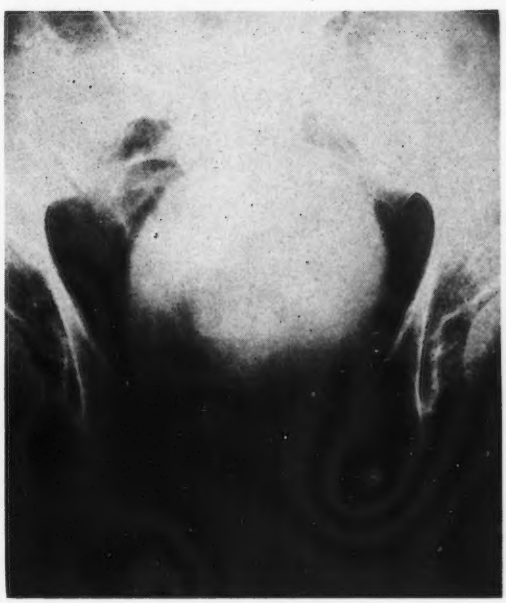


Figure 7

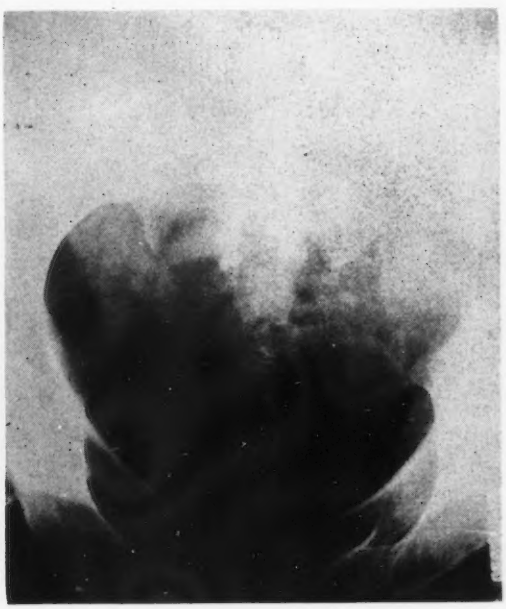


Figure 8

full bladder which was relieved by voiding. These symptoms were typical of Hunner ulcer, which was found and permanently cured by several treatments of overdistending the bladder.

Figure 10. A large unsuspected residual of 400 cc.

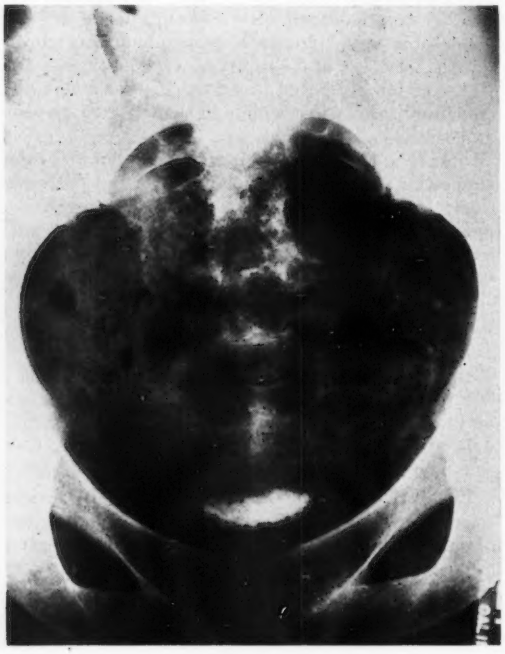


Figure 9

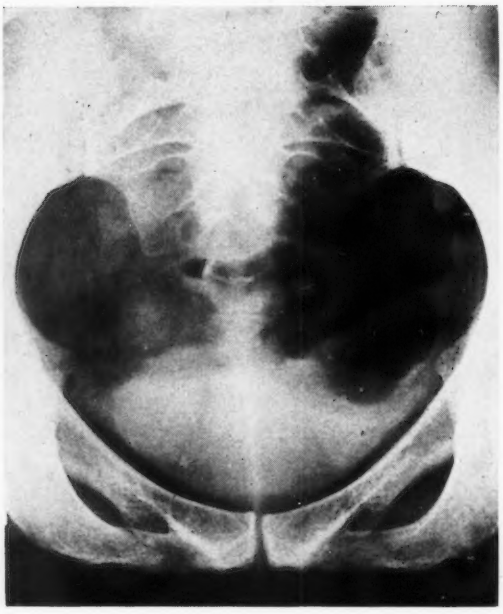


Figure 10

of urine in a female, the mother of three children, who had been treated for nervousness for years. She had had previous excretory urograms, as well as cystoscopic examinations, and a residual urine never had been determined previously. She had very little evidence of a cystocele, but a contracted bladder neck was present. Since operation was refused, several urethral dilatations with a Kollman dilator were carried out and gave a great deal of symptomatic relief. Subsequently the urine became clear and bladder symptoms disappeared.

* * *

GROUP 4. Filling defects of the bladder not due to primary neoplasm.

A negative excretory cystogram does not exclude the possibility of neoplasm of the bladder, and it is to be emphasized that there is positively no excuse for not cystoscoping every patient with hematuria and making an attempt at early discovery of its source. Most bladders with moderate sized neoplasms can empty completely unless the bladder neck is involved in such a way as to cause residual urine. If there is no residual urine, the filling defects are best noted in the preliminary series of films, all of which should include the bladder, as was emphasized in the outline on technique in Table 2.

Figure 11. Filling defect in the region of the right seminal vesicle due to a large retroperitoneal abscess, which started from osteomyelitis of the lumbar vertebrae pointed in the costovertebral angle, causing fixation of the right kidney and extending down into the pelvis on the right side of the bladder. The clinical picture was characteristic of a perirenal abscess.

Figure 12. Excretory cystogram of the same patient (Figure 11) two months after drainage of the

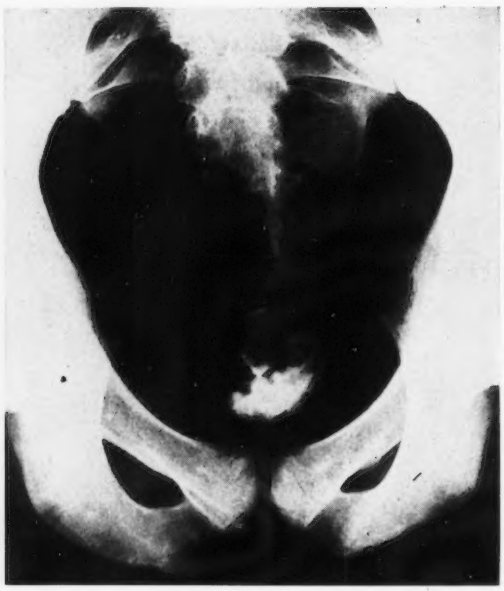


Figure 11

abscess, apparently stenosing the orifices of the seminal vesicles and leaving them in a dilated cystic condition, showing as a characteristic outline. The ureters are pushed upward to some extent.

Figure 13. Filling defect of the bladder caused by a large diverticulum, not diagnosed until the patient was cystoscoped. The fact that there is residual urine indicates bladder neck involvement, which was found to be of a fibrous contracted type. This film also shows that a diverticulum does not fill unless the orifice is large enough to admit the diffusion of the opaque urine.

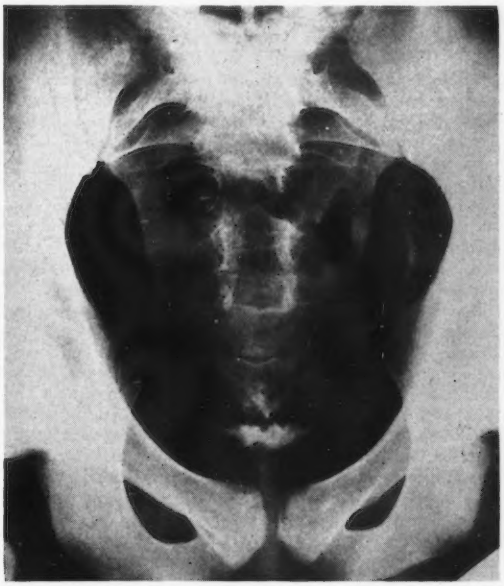


Figure 12

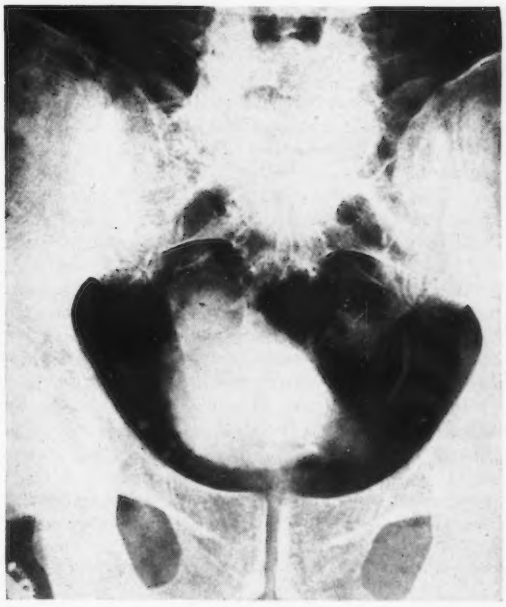


Figure 13

Figure 14

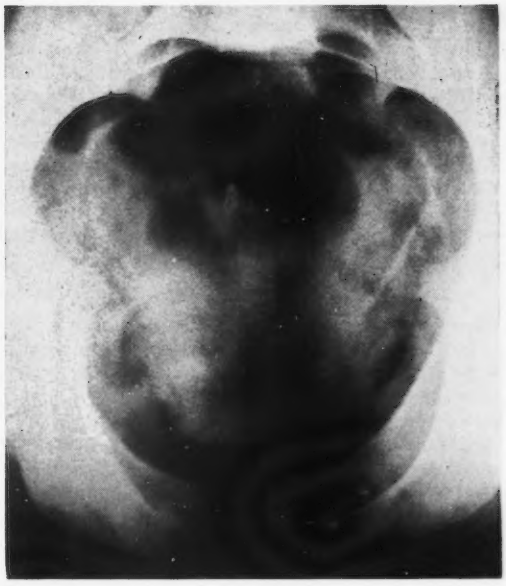


Figure 15

GROUP 5. At times the lower ends of the ureters are best visualized and studied in excretory cystograms.

Figure 14. This film shows the ureters dilated to the bladder wall, due to chronic vesiculitis and prostatic stones.

Figure 15. This is the only film in the series to show a non-opaque stone in the lower end of left ureter, later delivered with Council Stone Basket.

SUMMARY

Not only should filling defects be kept in mind and studied in after-voiding excretory cystograms, as indicative of hypertrophied prostates, bladder tumors and pressure from outside sources, but also attention must be paid to the developmental changes in the bladder wall resulting from obstruction and from abnormal stimulation such as urethral polyps, Hunner ulcers, cystitis, and stones.

DISCUSSION BY A. M. MEADS, M.D.

Doctor Dillon's paper has emphasized to me a step in intravenous urography that for the most part I have been neglecting. So partial have I been to retrograde studies of the urinary tract due to the abuse of the intravenous method in the hands of the rank and file that I have used intravenous urography only as an adjunct to the retrograde studies. Personally I would not operate upon a case diagnosed by intravenous pyelographic evidence only, unless the findings were positive without the shadow of a doubt and the use of the retrograde method impossible. About two years ago within an interval of a few months we picked up two symptomless papillary carcinoma of the bladder while investigating cases of hypertrophied prostate. I am sure anyone would have missed these tumors if a cystoscopic investigation had not been carried out. Pyelographic fluid not infrequently obscures soft stones that have been interpreted by the roentgenologist as intestinal shadows, but which are revealed in their true relationship to the bladder by the cystoscope. Having a patient void during an examination is not always a simple matter, especially when he has been without fluids for a few hours and is of a nervous temperament. Such patients after a struggle may void only a small amount, leaving enough in the bladder to be misinterpreted as a residual when it is not.

If Doctor Dillon has solved the gas prob'em in intravenous urography, I congratulate him. This is not so important of course in bladder plates, but it often obscures the pelves and ureters on one or both sides just sufficiently to prevent a positive diagnosis. Recently I saw a so-called renal tumor scheduled for surgery which was proved to be normal by retrograde studies. I heard Doctor Braasch say in one of our recent prewar conventions that he considered only 40 per cent of intravenous urograms satisfactory enough for a complete diagnosis.

Doctor Dillon has emphasized the importance of preparation before x-ray films are taken. All urologists realize this, but many internists and general men do not. In spite of our routine that is supposed to free the intestine of gas, we still have many unsatisfactory films. We have avoided enemas because they seem to add insult to injury at times.

Intravenous urograms are either good or bad. The less the disease, the better the film is apt to be. At best, intravenous urography never tells the whole truth as to the condition of the kidney urine, the true function of the kidneys, or the conditions of the mucosa of the posterior urethra or the bladder. I feel, therefore, that when intravenous urograms are ordered their limitations should be considered from the point of view of a diagnosis and the point of view of the patient's pocketbook. Most patients, after paying for a complete intravenous study, wonder why the urologist demands a complete retrograde study.

These remarks are in no way critical of Doctor Dillon, for I know that he uses intravenous urography in selected cases. He has emphasized to me the part of my intravenous studies that I have neglected, namely, the last film showing the bladder after the patient has voided.

Management of Cardiospasm*

RUDOLPH SCHINDLER,† M.D., *Los Angeles*

THE clinical picture of cardiospasm is well known. Most physicians know persons who almost constantly are tortured by severe substernal pain, dysphagia and regurgitation of food. These symptoms usually render the patient unable to participate in any kind of social life. Eating in the presence of others becomes unfeasible, every attempt at swallowing food is accompanied by torturing distress and the patients become emaciated. Although death sometimes does occur as a result, it is relatively rare and frequently patients will be seen who have not been able to swallow normally for 25 to 30 years.

It seems that the fact that this disease is almost always curable is not as well known as the symptomatology. Time and again we encounter patients who have been treated with various methods without finding more than temporary relief. Such unsatisfactory treatment may even take place in our well equipped medical centers, and the procedures which could lead to complete cure are seldom carried out, obviously because they are unknown to the majority of the practitioners. In the following, neither the symptomatology nor the etiology nor the theories about the mechanism of cardiospasm will be discussed, but only the question of its management. There are four methods of treatment which require consideration, namely, (1) psychotherapy; (2) introduction of bougies through the spasm; (3) brusque dilatation of the spasm, and (4) surgical procedures.

1. *Psychotherapy:*

I believe I have been the first author to point to the frequent purely psychogenic etiology of cardiospasm. In fact, in 1926,[3] I was so convinced of this etiology that I believed that all cases of cardiospasm were of psychogenic origin. Quite typical situations were found to precede the outbreak of the disease picture, especially emotional upset which had to be suppressed, "swallowed down" as it were. One patient, a soldier, was observed who had had an attack of acute gastritis in the first combat line. His staff sergeant, whom he could not contradict, had looked upon his vomiting as malingering, and he then developed the full-blown picture of cardiospasm. Such cases were seen so frequently that I believed I had the right to draw the conclusion that all cases of cardiospasm had a common psychogenic etiology. Already then it was found that the underlying emotional disturbances were not attached to very deep layers of the subconscious and that they very rarely constituted a part of a major psychoneurosis. On the contrary, if present, these emotional disturbances are superficial and easy to recognize. Later I had to revise my opinion substantially.

It is true that some cases of cardiospasm are probably of purely psychogenic origin and—rarely—they are even connected with major psychoneuroses. There are many others, however, in which it is impossible to demonstrate clearly specific psychogenic factors. I have come to the conviction that many cases are of a purely somatic nature, the mechanism of which will not be discussed here. However, the question comes up whether or not some or all of these cases can be treated by psychotherapy. There is unanimity that this is not possible once the disease picture is fully developed. It is true that in the first few weeks simple suggestive treatment or hypnotic treatment may lead to a complete cure in some cases, but later a true conditioned reflex has developed, and psychotherapy then is useless even in cases in which the psychogenic character is manifest.

2. *Introduction of Bougies Through the Spasm:*

Before the mechanical procedures are discussed it should be stated that drugs of every kind are almost useless. Neither antispasmodics nor nitrates have any appreciable effect. Most frequently bougies and tubes of various kinds are used. Simple French elastic bougies may be introduced. Mercury bougies have been recommended, or blunt olives fastened on a whalebone staff. In occasional cases cure may be obtained by these measures, especially if exceedingly thick bougies or olives are used, but in the great majority they effect only a transitory relief. Manipulation in the depth of the dilated esophagus is never entirely devoid of danger and therefore there is no justification whatsoever to retain such unsatisfactory methods if much more successful methods are at our disposition.

3. *Brusque Dilatation of the Spasm:*

The true cures usually are possible only by brusque dilatation. This procedure has sometimes been called "stretching" of the esophagus, an unfortunate term. The fact is that the muscle fibers forming the constricting ring must be forcefully torn apart under the intact mucosa. If one succeeds in doing this, and only then, is an immediate cure without recurrence obtained. Different types of instruments have been described. Most widely used are the pneumatic and hydrostatic bags of Plummer,[2] Fitzgibbon[1] and others which are introduced at the tip of a tube into the cardia and which then are dilated either by inflation of air or by water pressure. Both air and

* Paper read before California Medical Association, May 8, 1946.

† From the Medical Department, College of Medical Evangelists, 1052 West Sixth Street, Los Angeles 14, California.

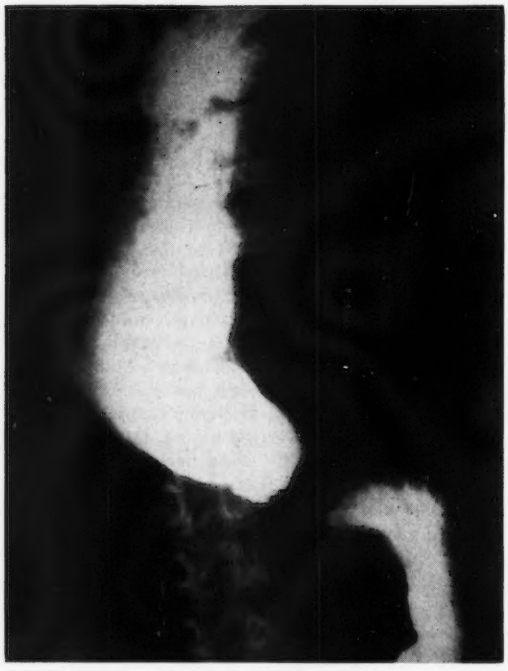
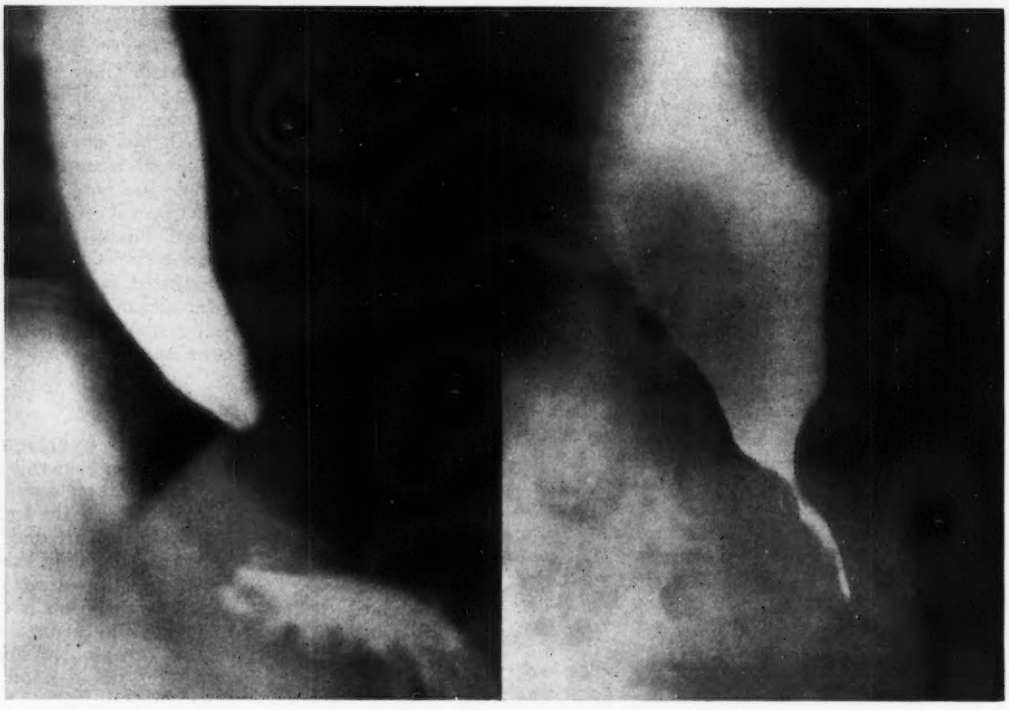


Figure 1.—*Cardiospasm.* Typical x-ray picture. Esophagus dilated and tortuous. Spastic constriction at the level of the diaphragm. Smooth outline of lower end of esophagus. Only small amount of barium in stomach.

water are filled into the bag under controlled pressure. With sufficient dilatation the musculature will rupture and cure will be obtained. The other type of instrument, the one which I personally recommend most, is the metal dilator which in folded condition is introduced so that it lies in the cardia and which then is fully spread in umbrella-like fashion so that its metal branches will brusquely dilate the cardia.

The appealing factor of the first method, that of the collapsible bag, is that its use looks rather simple. After its introduction air or water has to be introduced into the bag and the necessary pressure is simply read from a manometer. This however, involves a certain danger. We have no means of knowing what happens to the tissues in the depth and therefore it is not too surprising that sometimes ruptures of the esophagus occur which lead to death. Manipulation in the depth of the esophagus is always a risky procedure and an expert working with a hydrostatic dilator is certainly less likely to have an accident than an awkward beginner with a metal dilator. Yet I feel that to the expert the metal dilator will have greater appeal because at any moment he is able to feel with his fingers what he is doing in the depth and what resistance is offered by the tissue. In order to have full and gratifying success with either method, slow and deliberate procedure is imperative.

First the diagnosis must be established beyond any doubt. It is true that the x-ray pictures usually are



A B

Figure 2.—*Two different types of cardiospasm.* In the case pictured at the left side the point of constriction is the hiatus of the diaphragm; in the case pictured at the right side the point of constriction is the cardia itself.

characteristic. Such a typical picture is shown on Figure 1. The esophagus is dilated and tortuous, its lower contour is perfectly smooth without any filling defect. It is of great practical importance that there are two different types of cardiospasm. Some authors have contended that the diaphragm itself forms the spastic constriction. Others have contended that the ring of the cardia is the narrowed point. Figure 2 shows that both types do occur. In Figure 2a the barium is stopped within the hiatus of the diaphragm. In Figure 2b the barium fills out the abdominal esophagus and is stopped in the cardia. The dilating instrument must lie exactly within the constriction and therefore it becomes necessary to measure out the exact distance between the narrowed point and the row of the teeth. This should be done under fluoroscopic observation with the dilating instrument itself.

Figure 3 demonstrates the metal dilator. The left side of the picture shows the closed instrument with an elastic rubber attachment, which guides it through the esophagus and through the cardiospasm, and with the handle the compressing of which opens the dilating portion of the instrument. On the right side of the picture the opening mechanism of the instrument is demonstrated. In contrast to scar strictures or tumors of the esophagus, which should be passed only over a thread, no thread is needed in cardiospasm. In true cardiospasm, bougies and instruments will enter the stomach readily. Different attachments may be used, a mercury attachment being preferable in unusually difficult cases. It is clear that such a procedure would lead to disastrous consequences if any organic obstruction is present. By all means organic obstruction must be excluded before a brusque dilatation is carried out. This is not always possible by x-ray.

Figure 4 shows the x-ray picture of a patient referred for treatment under the diagnosis of cardiospasm, and this picture looks indeed rather characteristic. However, the peculiar behavior of the patient, his impatience, his rather uncooperative

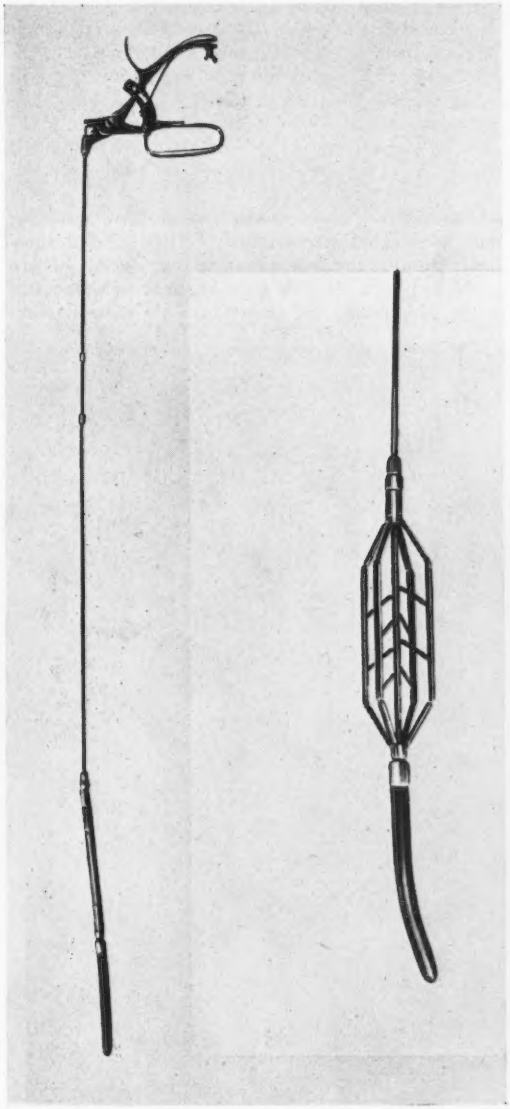


Figure 3.—*Metal dilator for the brusque dilatation of the cardiospasm.* Elastic attachment to the gastric side of the instrument. Dilating mechanism closed in left portion of picture; opened in right portion of picture; handle at upper side of picture permits sudden brusque opening of the instrument.

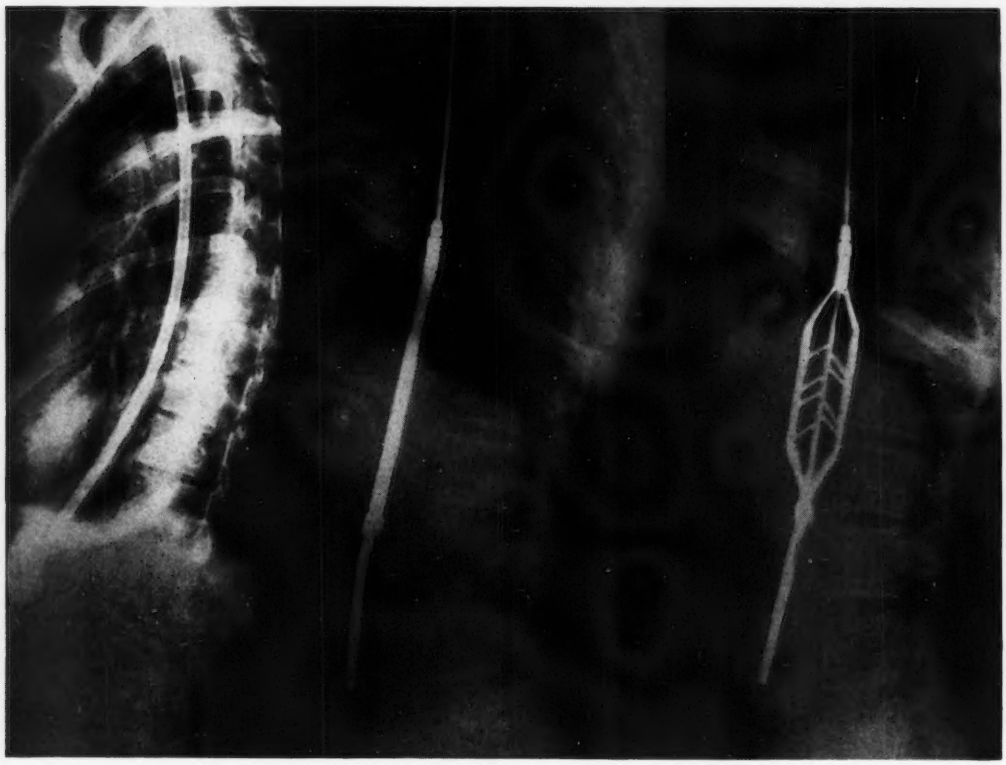
Figure 4.—X-ray picture of obstruction of the cardia simulating cardiospasm. The patient had a carcinoma. (See text.)

manner caused doubt about the diagnosis. Esophagoscopy was recommended and carried out. No organic lesion was discovered. On the whole, gastroscopy is the best endoscopic method for the exploration of a cardiospasm. The dilated bag of the lower esophagus can be observed readily through the gastroscope which then will enter the stomach without difficulty and which will permit visualization of the fornix of the stomach. In the case pictured in Figure 4, the gastroscope at two attempts refused to enter the stomach although a thick bougie did enter. Thereupon the further procedure was given up and the diagnosis held in abeyance. The patient was explored and carcinomatosis of the abdominal cavity was found.

The course of the procedure is as follows:

First the patient is x-rayed carefully, in various directions and under the use of numerous spot films. If then the diagnosis or cardiospasm seems to be fairly well established, he is trained to swallow tubes of different sizes. His throat should be anesthetized before each such procedure, as he will cooperate much more reasonably and quietly if the gagging and retching reflex has been suppressed. Each time, the esophagus should first be emptied through a simple Ewald tube by gravity. This draining of the esophagus permits quiet working which otherwise would be constantly disturbed by vomiting and retching. The possibility of introducing even very large bougies does not establish the diagnosis of cardiospasm beyond any doubt. In the case of carcinoma just described a French bougie Number 45 entered the stomach quite readily.

The next step therefore is gastroscopy. If at gastroscopy no organic lesion of fornix, of the stomach, of the upper lesser curvature of the stomach, of the cardia and of the lower esophagus has been found, the diagnosis finally can be considered as established. The next step is the preliminary introduction of the dilating instrument and the measuring of the distance between teeth and the narrow and obstructing ring before the fluoroscope, a difficult procedure. The patient then is hospitalized after having been prepared for several days with sulfa drugs. His esophagus is washed out and some sulfa drug is injected intravenously. After careful anesthesia the dilating instrument is introduced. Figure 5a shows on the left side a simple Rehfuss tube lying in the esophagus and stomach, with some barium



A B C

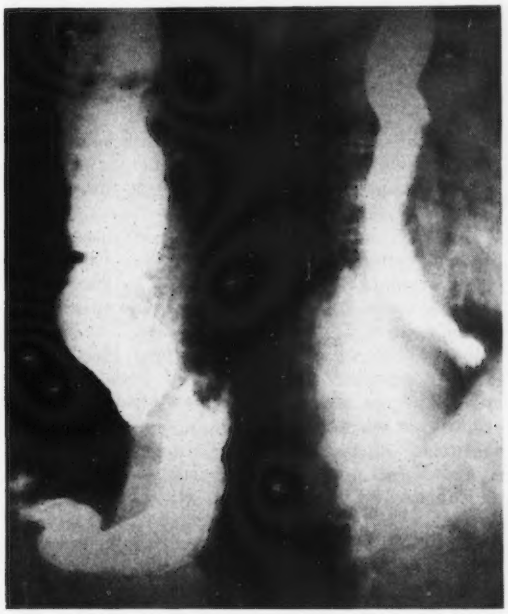
Figure 5.—*Brusque dilatation in a case of cardiospasm.* (a) X-ray picture of the patient with Rehfuss tube in stomach; barium indicates the location of the spasm at the cardia below the diaphragm. (b) X-ray picture of same patient, the metal dilator having been brought into the correct location. (c) X-ray picture of same patient. The brusque dilatation being carried out; the branches of the dilating instrument are spread and disrupt forcefully the musculature of the cardia under the intact mucosa.

indicating the place of the narrowing. The dilating portion of the instrument has to lie in this place. Figure 5b shows the closed instrument introduced, and Figure 5c shows the opening of the instrument within the narrowing ring of the cardia.

When this maneuver is executed the patient experiences a sharp pain. The success, however, is not dependent upon the amount of pain the patient feels.

A B

Figure 6.—Patient before (a) and after (b) brusque dilatation of cardiospasm.



A B

Figure 7.—*X-ray pictures of the esophagus in a case of cardiospasm.* (a) Before treatment. (b) After treatment. In this case the esophagus has shrunk to an almost normal size. More frequently it does not return to the normal.

Until a short time ago I was convinced that success could be obtained only when the constricting ring is caught in the condition of spastic contraction. The hand of the operator will feel a most marked resistance which has to be overcome with a certain amount of force and which causes a most disagreeable feeling of tearing apart of tissue. I still feel that usually success is obtained only if this sensation is felt by the hand of the operator, and that if no resistance is felt there will be no success and the procedure has to be repeated in a week or so. In most cases the cure succeeds in one single session. In some additional cases two dilations may be necessary and in one case five sessions were needed until finally the constricting musculature was caught in a condition of spasm. Quite recently however, a case was observed in which the operating hand did not feel any resistance whatsoever and in which, nevertheless, complete cure was obtained.

The patient is observed for one day and when on the next day he tries to eat his breakfast he will be able to swallow without any difficulty for the first time in many years. This success as seen with the eyes of the patient is overwhelming and I do not know of any patient who is more grateful than the patient treated for cardiospasm.

The result is usually a dramatic one. The patient starts picking up weight at once. Figure 6 shows a patient before and three months after treatment. Formerly I believed that in spite of the good results the esophagus would never shrink to normal size again, but more recent experiences have made me more optimistic on this point. Figure 7a shows a case of cardiospasm at the time of the operation. Figure 7b shows the same esophagus eight months later. It has shrunk to about half its former size.

The results are shown in Table I. One case remained uncured, a 24-year-old girl in whom repeated dilation with every type of dilator was unsuccessful. Unfortunately she had a severe mitral stenosis so that thoracic surgery could not be undertaken. In one case there was a probable recurrence.

A complete success was obtained in 24 cases, which is a total of 92.3 per cent. No fatalities have occurred in this series and only three minor complications were seen. In two cases there was some peritoneal irritation which subsided after two days. The vagus shock observed in another case, lasted only a few minutes.

4. *Surgical Procedures:*

The fourth therapeutic possibility, that of thoracic surgery with esophagoplasty, will obviously become necessary only in most exceptional cases. It may

TABLE 1.—*Cases of Cardiospasm Treated with Brusque Dilatation*

Failure	Probable Recurrence After Cure	Complete Success	Total	Fatalities	Complications: Mild Peritoneal Irritation	Complications: Vagus Shock
1	1	24 (92.3%)	26	0	2	1

be, however, that a patient suddenly gets a complete occlusion so that not even a drop of water may pass the cardiospasm. Then gastrostomy must be performed if no expert is at hand able to carry out the described method of dilatation. In Paris, this writer treated a man who for ten years had been lying in the hospital of Vaugirard with a stomach fistula and who had been fed constantly through this fistula. He was cured by one single brusque dilatation. It is my opinion that we can avoid seeing such cases by the use of the proper procedure.

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California's Plan for the Study and Control of Mosquito-Borne Diseases†

By LESTER BRESLOW, M.D., M.P.H.,* *and* ARVE DAHL, M.S. in San. Eng.,‡ *San Francisco*

THE California legislature has initiated an extensive program for the prevention of mosquito-borne diseases by appropriating $600,000 for this activity during the present biennium. In the Act it was recognized that further research is necessary to increase the effectiveness of such work. The purpose of this discussion is to describe the administrative approach to this rather complex epidemiologic and disease-control problem. Results of the first year's investigative activities wait upon laboratory examinations now being conducted.

Written records of mosquito-borne disease in California extend back to the days of '49 when malaria was a scourge. Military reports[2] for July-September 1853 state that the incidence was 816 cases per 1,000 men in Northern California posts. Malaria continued to be a major health problem for decades; as late as 1909, Dr. William F. Snow, Secretary of the State Board of Health, termed it the "minataur" of California.

In 1903, the first mosquito control work in California was undertaken in San Rafael. Sufficient interest was aroused for the passage in 1915 of a Mosquito Abatement District Act which provided that a community could organize its territory into a mosquito abatement district, with funds provided through a tax levy limited at first to 10 cents (now 40 cents) on each hundred dollars of property. During the ten years following passage of this Act, 15 districts were organized and the incidence of malaria dropped 90 per cent—from a case rate of 17.9 to 1.7 per 100,000.

However, another mosquito-borne disease has become prominent in the Central Valley. Encephalomyelitis was first recognized there in 1930 when approximately 6,000 horses and mules were affected, with a 50 per cent mortality. The malady reappeared in subsequent years, Meyer, Haring, and Howitt[3] reported the isolation of a virus as the etiologic agent which later became known as Western equine encephalomyelitis.

Human encephalitis in California, following World War I, occurred primarily in urban areas and during the winter months. It declined to a low point in 1933. Thereafter, the reported incidence of encephalitis began to rise again but the character of the disease was quite different: it was largely a summer disease and appeared in the same rural areas where equine encephalomyelitis was known. Studies[1] proved that the Western equine and St. Louis viruses cause human as well as horse disease and that mosquitoes are a vector. One thousand, three hundred and eighty-three human cases and 453 deaths were reported during the ten-year period 1936-1945. The state was also faced with a possibility of serious human outbreak, such as the midwestern experiences, and the possible importation of Japanese B encephalitis.

Besides the concern with this disease picture, water and power development and expanding

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* Division of Preventive Medical Services, California State Department of Public Health.
‡ Division of Environmental Sanitation, California State Department of Public Health.

irrigation areas were constantly adding new elements to the mosquito control problem. There was also a popular fear of the spread of malaria from returning veterans.

RECENT LEGISLATION

With the above considerations in mind the State Senate asked for a report by the Department of Public Health on the disease-bearing mosquito hazard in California. Following submission of the report the Legislature in 1946 enacted a bill "to provide State Assistance of local agencies for the control of mosquitoes," on a 50 per cent matching basis. The Department of Public Health was authorized to "enter into cooperative agreements with any local district or other public agency engaged in the work of controlling mosquitoes . . . under such terms . . . as the State Board of Public Health may prescribe." Of the $600,000 appropriated, it was specified that not more than $200,000 was to be spent for studies, demonstrations and administration.

In order to clarify the detailed operations of this program, it is necessary to mention that the California State Department of Public Health includes five divisions—Local Health Services, Administration, Preventive Medical Services, Environmental Sanitation and Laboratories. Bureaus of the latter four divisions all participated in the study program to be described below.

SUBVENTION PROGRAM

The Mosquito Control Section of the Division of Environmental Sanitation was assigned responsibility for allocating the subventions. A staff of engineers and entomologists was assembled to carry out the program and an Advisory Committee established with representation from the University of California, the Hooper Foundation, local health departments and mosquito abatement districts, to assist in establishing criteria for alloting funds.

In applying for funds, a district was required to submit a statement on the prevalence of malaria and human and equine encephalitis, to prepare a map of the district showing cases of the preceding five years and the proposed disease-control area, to present a budget, and to state the qualifications of the person having technical responsibility for the program. The applications were, of course, designed to emphasize the disease-control aspects of mosquito abatement and to bring the districts into close relationship with the health departments. Criteria for allotment of funds included extent and severity of the disease problem and known prevalence of vectors.

The premise of his program is that mosquito control offers the most promising approach to the control of encephalitis, as well as of other mosquito-borne diseases.

Staff members of the mosquito control section assisted the districts in formulating their applications, expanding their programs in accordance with the latest epidemiologic information and developing entomologic controls for their work.

STUDY PROGRAM

In spite of the strides made during the past decade, our knowledge of the epidemiology of encephalitis has numerous gaps. Are there any reliable clinical differences between encephalitis and non-paralytic poliomyelitis? In recent years, comparatively few cases clinically appearing as encephalitis have been proved due to any of the known viruses. Are other agents involved? From what host does the mosquito acquire the virus and how does the virus persist through the winter? Which of the mosquitoes already implicated is most important, and are there others? What is the most economical way of destroying the known vectors?

In an effort to get further data on these questions, the State Department of Public Health created an intra-departmental committee. Representatives from the fields of epidemiology, veterinary medicine, virology, engineering, entomology, statistics and health education contributed to the plan and met bi-weekly during the season to check on its implementation. This served to bring persons with varied responsibilities into effective cooperation for this one activity.

Before the seasonal rise in incidence occurred, an educational campaign was conducted in order to acquaint appropriate persons with the study and to gain their cooperation. The campaign included visits to mosquito abatement districts, health officers and hospitals, addresses to medical societies, personal contacts and addresses to veterinarians, articles in rural newspapers and journals, and radio programs.

In charge of the office from which the study project operates was placed a statistician who also had responsibility for the development of suitable records.

Health officers report human cases by telephone or teletype. Telephone communication is maintained with epidemiologists in the field who investigate each case. Equine cases are similarly handled, being seen by the veterinarian on the staff. Blood and tissue specimens are submitted to the virus laboratory. All cases are referred to the Mosquito Control Section for entomologic observations.

To indicate the volume of field work this first summer, it may be mentioned that detailed epidemiologic histories were obtained on 136 human and 90 equine cases, and 380 blood and tissue specimens secured from these cases.

In addition to the investigation of equine and human cases, two other field studies were undertaken. One was the collection of suspected vectors and suspected reservoir hosts. A mobile laboratory unit secured specimens from 675 birds and animals, including wrens, owls, pheasants, mud-hens, finches, squirrels, gophers, field mice and many other species. The second project was to study mosquito ecology and to evaluate various methods of control.

Besides these activities of the State Department of Public Health, it should be noted that the fundamental studies of the Hooper Foundation were continued in Kern County, this year, with partial subsidization from the State funds. In several respects, the model for the state program had been established by the Hooper Foundation in previous years.

Although the concentration was on encephalitis, malaria was not overlooked. Data were routinely secured on probable source of infection and preparations were made for investigating any outbreaks. None have occurred as yet.

PROGRESS

Following passage of the legislation, a technical staff of 17 people had to be assembled and trained, the program defined and field work conducted. Investigative results will be reported after completion of laboratory work.

However, certain administrative accomplishments may be mentioned. Of the $400,000 available for subventions to abatement districts, $358,613 has already been allotted. Area covered by mosquito abatement districts in the state has been increased from 4,645 square miles to 10,927 square miles. In addition to this extension of mosquito control activities, the quality of work has been improved by emphasis on disease-prevention aspects, by stress upon adequate technical supervision, and by demonstration of new methods.

Wider recognition of the services of the virus laboratory has been reflected in the greatly increased numbers of specimens submitted by practicing physicians and veterinarians. Clinical consultation service has been well received and has probably enhanced the reliability of reported incidence of neurotropic virus diseases—both human and equine.

The liaison established between the Department of Public Health and veterinarians holds the promise of collaboration against other diseases of mutual interest such as rabies and brucellosis. Steps in this direction are now under consideration.

In summary, it may be stated that a start has been made in applying all the resources of the State Department of Public Health toward the solution of the problems involved in the eradication of mosquito-borne disease, in accord with the present trend toward collaborative research.

As a pattern of intra-departmental organization, the encephalitis program offers an example of planning and carrying out an extensive project involving laboratory, epidemiologic, environmental sanitation, statistical and health educational services. A similar pattern is expected to prove useful in attacking murine typhus, relapsing fever, brucellosis and other diseases.

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Some Features of Psychiatric Practice in Postwar Medical Care Planning*

H. E. CHAMBERLAIN, M.D., *Sacramento*

RECORDED history reveals that in the wake of war, man's confidence in mankind's intent to cooperate—individually or internationally—invariably diminishes and the feeling of guilt and distrust between men mounts. The present postwar period already contains ample evidence that these days are not to bring an exception.

Fragmentary reports of the state of mind, both singly and in the congregate, of those in defeat appear to indicate several clear-cut characteristics which are at variance in degree only with characteristics to be observed in the state of mind of those round about us and in victory. Briefly, these characteristics are:

1. *Despair*—be it of food or shelter or economic security or political expression or domestic compatibility.
2. "*Shock*"—be it in relation to an episode or a benumbing drift, wherein the individual (or his group) is dazed or absorbed in a day to day existence and permits or expects others to assume responsibility for his survival and also to provide a directional force to his liabilities.
3. *Disillusionment*—in goals, in principles and in people.
4. *Hatred*—which may be so diffuse and unfocused that it is taken out on anybody or on everything.
5. *Shame (or Guilt)*—wherein assault and truculent attitudes compulsively serve as a disguise and everybody or anything becomes a potential target. (On the battlefield, and whether or not in association with guilt, this characteristic is capitalized upon in the strategy of "the best defense is to attack and then to attack again and again.")
6. *Fear*—that is cloaked in uncertainty, with its resultant—a truncated morale.

The reactions to these characteristics are well known to those of you in clinical practice. For orientation purposes only and without further comment they may be listed, too, as: (1) Callousness; (2) Deception; (3) Demoralization (planlessness); (4) Docility ("vacuity")—intellectual, moral, politic, etc.; (5) Self-pity.

Although we see these characteristics of the state of mind in our erstwhile enemies, in the reactions to those characteristics we now observe much of ourselves. This universality of the characteristics of mental life in the wake of war, in the enemy or the ally, and the limited but far-reaching reactions in people or in governments to those characteristics must be respected and sharply observed in whatever program the practice of psychiatry is to function. The implication is plain: a broad basic interpretation of psychiatric concepts (with supplemental coloration by neurology and psychoanalysis), unidentified with a clinic *per se* or diagnostic pathologic analogies, must be repeatedly offered to the *mass* population which is distraught not only by personal aberrations but also by economic insecurity, political intrigue and feelings of religious betrayal.

Psychiatry is being widely heralded through the periodicals, the press, the movies and the radio. On the whole, it may be contended safely that much that is presented is good rather than bad, and that the public's reaction to it is generally favorable. There is grave doubt, however, that other professions are as favorably disposed. And though it is evident that extensive interest in psychosomatic medicine, in geriatics, in anthropologic research and in socio-economic analyses may assist psychiatry to become free and untainted to men at large—there are such indications here and there—nevertheless, increased unchecked alcoholism, extensive sex irregularities, and grossly compromised family patterns may serve to fetter psychiatry with even greater stigma than it has formerly known.

Today in California a great impetus to professional standing and training has been given by the establishment of the Langley Porter Clinic in San Francisco and by the extensive practical revision of the program of the Department of Mental Hygiene. There are other signals too—though not many—that a few short progressive strides will be tried, albeit hampered by slender budgets. These hopeful signs are referred to in order that we may not be too discouraged that the mill still grinds exceedingly slow.

Psychiatric practice, if it be such, must broaden to be more widely available and accessible to vocational placement and family counseling. Four features of family life in America that have immeasurably altered the home and child rearing should be seriously studied and appraised by psychiatry for their emotional impact alone on personal adjustment. This should be done either in close cooperation with case work or nursing care or health insurance or court action. The four features are:

1. Increased mobility and unrest.
2. Reduction in number of offspring, giving par-

* Chairman's Address delivered before the Section on Psychiatry at the Seventy-fifth Annual Session of the California Medical Association, Hotel Biltmore, Los Angeles, May 7-10, 1946.

ents more free time and therefore: (a) a feeling of duty to inform themselves as to child development and training, (b) an obligation to apply the information, and, hence (c) a greater sense of guilt if they should fail in that obligation.

3. Emancipation of womanhood with its higher education status and its keener occupational rivalry not only with men but also with its own.

4. Impact and influence of fourteen and more millions of ex-service personnel conditioned to rank, prerogatives, authority, rumor, indulgences, "gripes," and congregate rivalries—all specific and to a high degree foreign to civilian life.

The impact of the ex-serviceman and its effect upon his kin are not restricted to the home; they extend also to industrial output and community planning. These men and women of the services speak out bluntly about psychiatry when counseled apart and away from signs of authority. The psychiatrists' rôle at selection and induction; what the chaplain has advised; what the field representative of American Red Cross or a USO volunteer has said; what the medical officer has inferred—all this has given a tint to psychiatry that is not bright. Disciplinary hearings and military police supervision and courts martial decisions far away from the simplest psychiatric tolerance are other factors operating detrimentally. Still others are the psychiatric interviews, however skillful or adroit or however leisurely conducted, that left the serviceman stuck with a coded diagnosis, or sent him out again into action, or rushed him back from the front to be discharged with a marked form to confirm to all that his signs of maladaptation were traceable to infancy or puberty or both. Moreover, if a veteran is left abandoned to a generalized policy of medical care in which every disability or symptom is evaluated alongside the possibility of claim for monetary compensation, or if standing in line-ups or in bureau waiting rooms with other veterans convinces him that his medical care is comparative and he must compete for it, or if even excellent treatment is permitted to lapse and delays occur which permit him to "shop about"—then he is likely to reach such an attitude as to make the application of psychiatric principles practically impossible and even to be looked upon as ridiculous.

Another barrier to the veteran's acceptance of the value of psychiatry is that in the armed services, shackled by countless administrative tasks or sitting in perfunctory review board hearings, psychiatrists grow weary and are not regarded at their optimal best.

Civilian attitude toward psychiatry will have much to do with its acceptance by the veteran. Few veterans will utilize psychiatric services constructively or with assurance unless these same services are observed to be widely applicable and extensively used by civilians. If a veteran does avail himself of treatment and the civilian population has a scoffing attitude toward psychiatry—especially psychoanalytic psychiatry—then he will feel that, even though benefited by the treatment, he is further stigmatized.

Several bills before Congress (if they are enacted), as well as the Dean's Committee plan of the Veterans Administration and other current proposals, may help to clarify within the next decade some of the drawbacks from an overall psychiatric point of view which are perpetuated at the colossal and pagan shrines to the Goddess of Insanity.

The solution to most conduct problems is not in the acquisition of an increased academic knowledge. Instead, if properly analyzed, it is found to rest in the adaptability that comes from close living with mature and reliable adults who have themselves lived widely, tolerantly and courageously, and who have compensated constructively for their many errors. Therefore, a comprehensive program of psychiatric concepts should be first introduced—in early life—through public health organizations and the more progressive channels of education and welfare.

Since children in America are becoming more freely expressive, since adults are becoming more sensitized to early signs of distress and since our detection devices for those in difficulty are being perfected, it can appear that our conduct problems are on the increase. There is so large a backlog of undetected problems that an initial upsurge of additional problems, rather than an abrupt diminution, should be anticipated from the first. In the public domain, this one feature of administrative planning—more revelation and less resolution of problems initially—perplexes the legislator and pleases the contrarily scheming politician more than any other single factor. But to temporize or to defer action in the face of need for action—though this might be politically strategic—is to expose a compromising weakness that even today's psychiatric techniques, advanced and promising though they may appear to be, cannot neutralize nor hope to excuse. For as the alleviation of malnutrition and the widespread control of disease and pestilence have become global, albeit self-protectively, and the application of known public health protective devices ever so alertly introduced into every cabin, so too must psychiatry envisage a broader rôle and become extremely sensitive to all human conduct, at home and internationally. To lessen infant mortality and to extend the life span for humans, all in one generation, and not be concerned over the more and greater hardships those humans will be called upon to endure, is the seduction of scientific principle of the worst order.

To be structurally sound, any community-wide planning for psychiatric interpretation and service should be founded upon a broad base. It cannot limit itself to the analysis and the solution of problems. Such planning should recognize and emphasize the revolutionary changes in American family life which are now taking place, and the obsolete American school patterns which are now latent, and the aspects of both which contradict rather than complement one another. Finally, the professions, too, must be brought to awareness of their own inherent conflicts and limitations which tend to obscure mutual respect and resources.

Post Office Box 933, Sacramento, California.

Official Medical Investigation of Deaths in Behalf of Public Welfare

ALAN R. MORITZ,* M.D., *Boston*

EVERY 30 minutes there occurs somewhere in California a death from causes or in circumstances such as to require a prompt and competent official medical investigation in the interest of public welfare. Approximately 18,000 such deaths occur in the state each year.

What kind of deaths are these that require investigation in the public interest? Why is it essential that they be investigated officially? How well are they investigated in California?

Deaths that require investigation in the interests of public welfare fall into two principal groups. One comprises the unexpected or sudden deaths of persons who were not previously recognized to be suffering from dangerous or disabling disease. The other group includes all deaths known or suspected to have resulted from violence of one kind or another. Together they comprise approximately 20 per cent of all deaths that occur.

Any unexpected death from obscure causes may turn out to have resulted from violence. Competent investigation of such cases frequently discloses not only that death resulted from unsuspected physical or chemical injury but may also provide sufficient information to establish the probability of accident, suicide or murder. Another possibility is that any unexpected death from unknown cause may be found to have resulted from some form of rapidly fatal communicable disease that constitutes a particularly dangerous threat to public health so long as its identity remains obscure.

How often does the investigation of sudden deaths from obscure causes disclose information of importance to agencies responsible for law enforcement or public health? Is it worth the cost and trouble?

In areas where such deaths are routinely investigated through a competent medical examiner's office there is ample evidence that the cost is small in comparison to the service rendered. Routine investigation reveals that between 5 and 10 per cent of such deaths result from entirely unsuspected violence of one kind or another. Sometimes the injury or intoxication responsible for death is such as to indicate the probability of accidental incurment. When such is the case, heirs of the decedent are often enabled to claim compensation that they would otherwise not have received. In many instances knowledge of the cause of the death makes it possible to take steps to prevent others being similarly injured.

Not infrequently death is found to have resulted from a murder that would otherwise have escaped recognition. Even though the investigation discloses that death resulted from natural causes, it is by no means uncommon to find that it was due to some unsuspected communicable disease. In such an event the investigation provides the health authorities with information that may enable them to take immediate action to stop the spread of the infection.

Why is it desirable that such medical investigations be conducted by a public official rather than by a private physician? A procedure that is undertaken in behalf of public safety and one that is often responsible for securing evidence that may provide proof of the guilt or innocence of persons suspected of murder is a function of government. It must have legal authority and it must be beyond suspicion of partisanship. It should be conducted with the highest possible degree of competence.

What kind of official investigation would have been made of the death of Timothy Burke† if it had occurred in an average medium sized city in California? Burke worked in a small factory and one of his duties was to degrease small metal parts by passing them through a solvent. One Sunday morning he wakened with what seemed to be an attack of flu. By night he was very ill. Monday morning a physician was called who found Burke anuric and jaundiced and advised immediate hospitalization. By Monday afternoon Burke was in coma and that night he died.

The case was referred to the medical examiner's office on the grounds that death had occurred unexpectedly (within 24 hours) from obscure causes. An autopsy was performed and established that Burke's death was due to the inhalation of a hydrocarbon solvent that he had used for the first time during the last week that he worked. As a result of the investigation the use of this solvent was abandoned until more effective protective measures could be installed and further exposure of workmen to it was prevented. Burke's wife received full indemnification for his death through Workmen's Compensation Commission.

Would the coroner's office as it operates in the average California community have afforded this kind of protection to the fellow employees and widow of the decedent?

What kind of investigation would have been made of the death of Mary Jones if it had occurred in a small town in California? Mary was four years old and was cared for during the daytime in a

* Professor of Legal Medicine, Harvard University.

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† Although this and the other cases cited are authentic, the names are fictitious.

small nursery school operated for the benefit of mothers who were away from home during the daytime. At about 4 o'clock in the afternoon Mary came in from play and complained that she did not feel well. Half an hour after eating a light supper she had an attack of vomiting followed by a convulsion. A doctor was called who said that he would be somewhat delayed in getting there but to put the child in a warm bath if she had any more convulsions. By 7 o'clock there were more convulsions and the parents started with the child for the nearest hospital, where she died in the admitting room. The parents volunteered that Mary had always been healthy but that for several days preceding her terminal illness had seemed to have a slight cold with some sore throat.

The case was referred to the medical examiner's office as an unexpected death from obscure cause. Investigation disclosed that Mary had died of acute meningococcemia. Prompt bacteriological investigation in collaboration with the local board of health disclosed that the type of organism responsible for Mary's death was identical to one that was recovered from a culture of the throat of the woman who operated the nursery school. The school was temporarily closed and appropriate measures were taken to prevent the spread of the infection. There is every reason to believe that the investigation of Mary's death saved the lives of other children and contributed importantly to the suppression of a dangerous epidemic.

How frequently do murders successfully masquerade as deaths from natural causes in California? Under California's present inadequate coroner's system a homicide rate of approximately 500 per year is reported. There are many kinds of fatal physical or chemical injuries that leave no external disturbances to indicate their presence. There are many communities in which a death would probably be certified as due to natural causes if (1) the fatal attack and death were unwitnessed, (2) if the body were found in a place where it might normally be expected to be, and (3) if there were no external evidence of injury. It is a reasonable inference that there are many communities in which murder would pass unrecognized if there were no external marks of violence. Certainly there are many ways of killing people that do not produce visible wounds.

Would the death of William Snow have been recognized as murder had it occurred in an average community in California? Snow was a middle aged bachelor who lived alone on a small plot of ground at the edge of a village. He did not have a telephone. A neighbor on a mid-afternoon errand found Snow lying partially clothed on his bedroom floor and was unable to rouse him. A physician was called who ordered him removed to a hospital where death occurred six hours after admission with a presumptive diagnosis of meningitis. No external evidence of injury was noted and no history was available.

The medical examiner's office took jurisdiction and found that Snow's meningitis was due to a stab wound of the head that had been made with some long slender instrument like an icepick. The wound in the skin was so small and so covered by hair that it had escaped notice. Subsequent investigation by the police led to the discovery of witnesses whose testimony eventually led to the apprehension of the murderer.

The foregoing cases are by no means unusual. They should suffice to establish the fact that no community can afford to ignore deaths from obscure causes on the presumption that such a death does not deserve official inquiry unless there are positive grounds for suspecting criminal violence.

Attention has been called to the fact that in addition to the sudden death from obscure causes another 10 per cent of all deaths are known or suspected to have resulted from violence. The reason for making a detailed postmortem investigation if death by violence is suspected but not proved is apparent. What justification is there for performing a compulsory postmortem examination if the cause of death is already apparent?

Mrs. Whitby was found dead in the woodlot behind her house with a through-and-through gunshot injury of the neck. There was no doubt as to the cause of death. The bullet had passed through her body and was no longer available for examination. It was learned (1) that Mr. Whitby had motive and opportunity to kill his wife, (2) that several days before the shooting he had borrowed a high velocity rifle and ammunition from a friend, and (3) that he lied to the police interrogator as to his whereabouts on the day of his wife's death.

What could further examination of the body be expected to contribute to the ends of justice? An autopsy was performed and small flakes of metal were found on the margins of a smashed vertebra. Analysis of these traces disclosed a type of alloy that was entirely different from that of the only ammunition that Whitby could have used. This evidence established beyond reasonable doubt that Whitby did not fire the fatal bullet. Weeks later it was discovered that her death was accidental and had been caused by a random shot fired by a deer hunter who was too frightened to report the accident when he discovered what he had done.

How well do the existing laws and practices pertaining to the coroner's office of California provide for a competent medical investigation of deaths in the interests of public welfare? In a recent survey of the problem by a joint committee of the American Medical Association and the American Bar Association it was concluded that throughout most of the United States medical science participates less effectively in the administration of justice than it does in any comparable country in the world. It concluded furthermore that to function effectively the office of coroner or medical examiner should have a professional and technical personnel (1) that is selected for and retained in

office under some form of the merit system, (2) that is compensated at a rate sufficient to attract persons of high professional caliber, and (3) that is routinely notified of and empowered to investigate every death due to violent or to obscure causes.

The survey disclosed that the cost of maintaining such a service in metropolitan areas is not significantly greater than that of the average coroner's office and should probably be between 4 and 6 cents per capita per year. It was found that the inability or unwillingness of communities to provide for a competent medical agency for investigating deaths due to violent or obscure causes predisposes to: (a) Non-recognition of murder; (b) unjust accusation of innocent persons; (c) improper evaluation of medical evidence bearing on the circumstances in which fatal injuries were incurred; (d) failure to acquire medical evidence which would be useful in the apprehension of criminals; (e) failure to acquire medical evidence essential to the administration of civil justice; (f) ignorance of certain otherwise preventable hazards to public health, and (g) the impairment of the value of vital statistics.

It would appear to be incumbent on the physicians of California to scrutinize the manner in which medical science is being utilized to investigate deaths in the interests of justice and public health and to take such steps as may be necessary to bring this important professional activity to a plane comparable with that of other forms of medical practice.

Parenteral Fluid Therapy During Prolonged Surgery*

GORDON C. LANGSDORF, M.D., *San Diego*

EXPERIENCE at an Army hospital in the zone of the interior where many surgical procedures were long, and the problems of dehydration and blood loss therefore intensified, emphasized the importance not only of careful supervision of supportive parenteral fluid therapy by the anesthesiologist but of a readily available blood bank and the advisability of forehanded preparation of the patient for transfusions.

Since a potentially dangerous loss of fluid is to be expected in long operations, this discussion concerns the prevention of dehydration, the use of saline solutions and plasma as temporary blood substitutes, and massive transfusions of whole blood during protracted surgery.

LITERATURE

One of the greatest problems for the anesthesiologist during prolonged surgical procedures is the fairly accurate estimation of the progressive blood loss and the evaluation of its immediate significance. There is no single reliable test or clinical sign of impending shock, especially in anesthetic and post-anesthetic states. Our conception of the amount of blood lost in the course of a given operation may be obtained by reviewing the studies of Coller,[4] and Gatch,[5] and others.[6, 7, 8] In 1924 Gatch and Little[5] reported the first study of blood loss during some of the more common operations in general surgery in which accurate measurement of the losses were made. Everyone who has done such studies has been impressed that the blood loss at operation is often several times greater than that estimated by the surgeon. This is particularly true of the constant ooze of blood from large vascular fields during difficult dissections. Alexander Blain[3] in 1929, in commenting on his experience with 3,000 transfusions, urged the preoperative correction of anemia and the immediate replacement of blood lost during operation and condemned delaying blood transfusions until after shock had developed.

Concurrently with the blood loss determinations, Coller and his associates[4] made observations of changes in hematocrit, hemoglobin and plasma protein concentration before, during, and after operation. They found no correlation between the amount of blood lost and simultaneous changes in hematocrit, hemoglobin and concentration of plasma protein immediately before and after operation, and concluded that these determinations cannot be used to estimate the need for blood volume replacement during and after operation. Obviously, if one wishes to know precisely the amount of blood lost in any operation one must depend on direct measurement. Since this is not practical, one must rely primarily on a knowledge of average losses to provide a basis for the replacement of blood loss during operation. Coller[4] further emphasizes that all loss over 300 cc. in healthy adults should be replaced and that all blood loss in operations on aged, undernourished, seriously ill or bedfast patients should be replaced with equal quantities of blood.

In Table 1 is shown the blood loss during operation studied by Gatch and Little.[2] Table 2 shows the blood loss in operations of various kinds in

* Read before the Section on Anesthesiology at the Seventy-fifth Annual Session of the California Medical Association, Los Angeles, May 7-10, 1946.

626 cases compiled from the literature by Coller and his associates.[4] Table 3 presents the blood loss during operations reported by Coller.[4]

Coller believes that not enough emphasis has been placed on the relation of the amount of blood lost to the total blood volume. He further points out that since the blood volume varies with the weight of the patient, it makes a vital difference whether a given amount of blood is lost from a large adult or from a small child. In Table 4 are shown some figures illustrating the relationship of a 100 cc. blood loss to the blood volume in patients of differing weights. A simple method of calculating blood volume is to allow 35 cc. of blood for every pound, or 75 cc. for each kilogram, of body weight.

In 1943 Frederick Allen[2] advanced some thought-provoking views regarding the use of large saline infusions intravenously as a temporary means of maintaining an adequate blood volume, compatible with life. He pointed out that in hemorrhage, just as in other forms of shock, there is an alteration of such a nature that large saline infusions are not quantitatively lost from the blood stream within 24 hours as they are in normal animals but on the contrary they may provide a volume of dilute blood sufficient to maintain life for hours or days. Thus plain physiological saline solution, when given in sufficiently large volume, may preserve life through an emergency or shock period until it is possible to obtain blood for transfusion.

TABLE 1.—*Average Blood Loss During Operations Studies by Gatch and Little*[5]

Appendectomy, McBurney	7 cc.
Thyroidectomy	208 cc.
Radical breast	710 cc.
Laminectomy, fractured spine	672 cc.
Nephrectomy	816 cc.
Hysterectomy	232 cc.
Cholecystectomy	87 cc.

TABLE 2.—*Blood Loss in Operations of Various Kinds in 626 Cases Compiled from the Literature by Coller et al.*[4]

Operations	Number of Cases	Blood Loss: Maximum, Cc.	Blood Loss: Minimum, Cc.	Blood Loss: Average, Cc.
Brain	30	2,150	487	1,084
Postganglionic neurotomy (trigeminal)	4	650	86	337
Spinal cord	7	1,264	107	626
Thyroidectomy	29	1,118	16	237
Other neck operations	3	410	105	230
Mastectomies, radical	20	1,272	254	732
Mastectomies, simple	5	220	180	200
Thorax	113	2,895	35	575
Splenectomy	2	990	160	525
Intestinal above sigmoid	11	230	10	81
Appendectomy	14	62	4	13
Sigmoidal, rectal, and anus	21	1,220	8	377
Hernia	13	306	11	74
Miscellaneous abdominal	6	546	14	218
Pelvic	30	680	22	266
Prostatic resections, transurethral	220	1,254	4	280
Kidney	10	1,144	130	372
Orthopedic	31	1,564	40	441
Stomach	41	650	45	233
Biliary tract	16	400	51	100

POSSIBILITY OF EXCESS OF SODIUM CHLORIDE

With the administration of sodium chloride, there is the constant potential danger of overestimating the bodily need for sodium. Such an excess of sodium chloride often results in fluid retention and in a urine volume that is extremely small in proportion to the fluid intake. It must be remembered that pulmonary edema is an immediate danger whenever parenteral fluids are given in excessive amounts or at an excessive speed. Allen[2] admits this danger, but believes that when a patient is suffering from the dangerous anoxemia associated with an inadequate blood volume following hemorrhage, life-saving intravenous administration of huge volumes of normal saline solution should be rapidly given until whole blood becomes available. Pulmonary edema may be combatted if and when it arises, but the inadequate blood volume with

TABLE 4.—*Relationship of Blood Loss to Total Blood Volume*[4]

Weight (lb.)	Total Blood Volume (cc.)	100 cc. Loss Expressed as a Percentage of the Whole
10	450	22.0
20	890	11.0
40	1,600	6.2
80	2,825	3.6
140	5,000	2.0
200	7,000	1.4

TABLE 3.—*Blood Loss During Operations Studied by Coller et al.*[4]

Operations	Number of Cases	Blood Loss: Maximum, Cc.	Blood Loss: Minimum, Cc.	Blood Loss: Average, Cc.	Total Volume %
Mastectomy, radical	4	1,091	529	821	17.7
Thyroidectomy	8	725	99	379	11.7
Biliary tract, secondary and plastic	8	1,455	158	594	14.6
Rectal, combined abdomino-perineal	12	686	183	410	9.5
Stomach, complicated	3	804	321	599	13.6
Chondroma, presacral	1	.....	.....	1,257	39.6
Thyroidectomy, intrathoracic	1	.....	.....	1,397	20.6
Sarcoma of shoulder and hemiscapulectomy	1	.....	.....	857	22.9

its resultant anoxemia must be first improved.

Adams and his coworkers,[1] who studied the problem of citrate intoxication in massive transfusions of whole blood, concluded that it would be practically impossible to duplicate clinically in man the rapid rate of administration of citrated whole blood or plasma necessary to result in citrate intoxication, since this would necessitate the giving of over 4,000 cc. of blood to a 70 kg. man during a five-minute period. Thus they demonstrated that a large margin of safety is present in massive transfusion of citrated whole blood or plasma when the administration is at a maximum rate currently employed in man (1,000 cc. per hour). They found that calcium gluconate was very effective in preventing or alleviating citrate intoxication when very large doses of citrate had been administered during a short period of time.

PRESENT STUDY

The situation encountered at an Army hospital offered unusual opportunity for observations on the problem of blood loss and replacement during operations, in that a large percentage of the cases were those requiring the notoriously long reconstructive surgical procedures. Of 2,602 operations performed between August 1, 1944, and August 1, 1945, 710 lasted longer than two hours and 84 of these took over five hours.

As preface to a relation of experience with these cases, it is noteworthy that the patients for the most part were in excellent physical condition. Their average age was 27 years and they were in a good state of nutrition, as they had convalesced from the fatigue, exposure, malnutrition, shock, and acute infection commonly encountered in forward medical units. Hence it may be assumed that measures found advisable with these patients are even more applicable, in long surgical procedures, to civilian patients, whose condition generally cannot be expected to be as good as that experienced in military personnel.

In reviewing experience in protracted surgery cases in the Army hospital, it should be pointed out that water is available for kidney secretion only after the skin, lungs and intestinal tract have taken up their prior rights. In prolonged operative procedures, in addition to the normal insensible loss of water from the skin and lungs, a surgical patient who is draped in the usual manner with sheets and towels and is under the rays of a battery of operating lights suffers an enormous fluid and salt loss during a five to ten-hour operation. In an Army hospital, this loss was particularly marked during the summer months when the temperature in the operating rooms, none of which were air-conditioned, often ranged between 90 and 100°F.

Loss of water by these avenues during a long procedure becomes all the more important because there is usually a deficient fluid ingestion throughout the immediate preoperative and operative period. This deficiency was anticipated and its effect lessened to some extent by forcing fluids whenever possible during the 24 hours preceding the immediate preoperative period, although the common preoperative order, "nothing by mouth after midnight," before general anesthesia was followed to safeguard against the aspiration of vomitus during the induction period.

During operative procedures, salt and dextrose solutions were found primarily useful for the correction of dehydration. They were not considered very effective as blood substitutes, as the elevation of blood volume and blood pressure through their use was looked upon as transient. Administration of salt and dextrose solutions by the intravenous route rather than by hypodermoclysis is preferred now that the problem of pyrogenic reactions has been successfully solved. Fluids administered intravenously are immediately available to the entire body, whereas the absorption of those given by clysis is slow and variable. The amount of these solutions given during an operation must depend upon the estimated loss of water and sodium chloride from the body. Usually in a five to ten hour operation during the summer months, it was found advisable to give three to five liters of solution intravenously. Of these, two to three liters consisted of 5 per cent dextrose in distilled water.

While no effort to satisfy caloric, protein and vitamin requirements was considered necessary during an operation, it was concluded that this should be included in the preoperative and postoperative care. Recently, amigen and nutramigen solutions have been used in increasing amounts both preoperatively and postoperatively in gastro-intestinal cases.

Although at first there was no blood bank at the Army hospital where these studies were carried out, it soon became apparent that such a facility was almost a necessity in order to insure immediate availability of blood in large amounts during operations on aneurysms, brain and spinal tumors, and extensive bone defects. One ten-hour operation, the transplantation of both ureters, required meticulous dissection of structures in a densely scarred and highly vascular field. During the procedure, three and a half liters of whole blood as well as two liters of liquid plasma, three liters of physiological saline solution, and two liters of 5 per cent dextrose in distilled water were given—a total of ten and a half liters of parenteral fluids in ten hours. Indicative of the extent of blood loss, the patient 48 hours later was found to have a value for hemoglobin of 48 per cent and 2,420,000 red blood cells, as compared with 109 per cent and 5,580,000 preoperatively. The plasma given to this patient was used as a blood substitute during the period when additional blood was being typed, crossmatched and drawn. This and similar cases demonstrated the need for a local blood bank, which was then established.

It was most reassuring to have the patient crossmatched with four to six bottles of bank blood before attacking an arteriovenous aneurysm of the sub-clavian artery and innominate vein. When

such adequate precautionary preoperative crossmatching with bank blood was done, no additional emergency crossmatching was needed during the operative procedure.

The Rh determination was done on all patients receiving transfusions, and only Rh negative blood was given to Rh negative recipients. This was deemed advisable to prevent possible transfusion reactions due to anti-Rh agglutinations developing in patients receiving multiple transfusions during repeated reconstructive operations.

RATE OF ADMINISTRATION OF WHOLE BLOOD

The rate of administration of the whole blood depended upon the estimated amount and rate of blood loss by the patient and on the response of the blood pressure and pulse to that loss. Falling of blood pressure and rising pulse rate were considered an indication for an increase in the speed of administration of blood. Sometimes circulatory failure led to a complete collapse of the veins, and gravity alone was insufficient to cause a free flow of fluid. Then it might be necessary to force the blood in rapidly under pressure, either by (1) the use of a luer syringe attached to the three-way stopcock of the intravenous apparatus, or (2) by rolling the tubing toward the intravenous needle, or (3) by using a blood pressure bulb placed on the blood flask air inlet tube.

Experience in the Army hospital re-emphasized the advisability of carefully placing one and preferably two large gauge needles or cannulae into appropriate veins in the forearm or ankle before an operation is commenced. These may be kept patent by allowing a very slow drip of solution to flow through them or by leaving a stylet in place until the needle is to be used. Not infreqently, veins in the arms or the site of operation are poor and the ankle veins are the only one available. If these are small and do not distend following dependency and the proper application of hot towels, a "cut-down" and placement of cannulae should be done before beginning such surgical procedures as craniotomy, aneursysmorrhaphy, laminectomy, etc. This preoperative delay to permit the introduction of a large gauge needle pays tremendous dividends when rapid lifesaving administration of blood or plasma becomes imperative.

CONCLUSION

In conclusion it should be reiterated that supportive parenteral fluid therapy is a constant responsibility of the anesthesiologist and, further, that salt and dextrose solutions are primarily useful for the prevention of dehydration. Saline solutions and plasma are useful as temporary blood substitutes, but the most satisfactory method of maintaining the good condition of a patient during an operation in which much blood is lost requires the continuous replacement of whole blood.

Blood banks are a necessity in the modern hospital where repair of arteriovenous aneurysm, pneumonectomy, extirpation of brain tumor, or ligation of a patent ductus arteriosus is no longer considered unusual. Without a blood bank there is a tendency not to administer transfusions when indicated, or, when they are given, to use inadequate amounts of blood.

212 Medico-Dental Building, San Diego.

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Ancient Chinese Surgery: Acupuncture

ALBERT FIELDS, M.D.,* *Los Angeles*

ACUPUNCTURE, or needle-puncture, is one of the nine branches of medical practice recognized by the present day practitioners of ancient Chinese medicine. It is a procedure peculiar to China and has been in use there from time immemorial. According to tradition, it was originated by the Yellow Emperor, Huang-Ti (B.C. 2698-2598). The technique and indications are described in The Internal Medical Classic, Nei Ching, supposed to have been written by Huang-Ti. Pien Ch'iao, a famous physician in the Fifth Century B.C., was skilled in its application. During the T'ang Dynasty (A.D. 618-907) special schools for instruction in acupuncture were established and several manuscripts on the subject were written. In A.D. 1027, by the order of the Sung emperor, two copper figures of the human body were made, with markings to illustrate the principles of acupuncture.

The purpose is to needle or puncture certain involved "vital points" (hsueh tao), to release "bad secretions" and relieve tissue obstructions. There are 365 of these vital points, corresponding to the days of the year. Each of these points has its own name and is assigned some relationship to the internal structures and to the circulatory system. Thus, this system of therapy as practised by the Chinese is dependent upon their concepts of disease and their "understanding" of the circulatory system.

It is of interest that perhaps the Chinese did appreciate the connection of the heart with circulation more than a thousand years before Harvey. In the previously mentioned Nei Ching it is written, "The heart regulates all the blood in the body . . . The blood flows in a circle and never stops." The Chinese have a theory of double circulation by which the "spirits," which are the vehicle of the Yin principle, and the blood, which conveys the Yang principle, are distributed through the body. The circulation begins in the lungs at 3 o'clock in the morning (the Hour of the Tiger) and completes the rounds in 24 hours. For the accommodation of this circulation they count twelve principal canals (Chin)—six pass from above downwards and six from below upwards. There are also accessory canals, eight of which run transversely and nine obliquely. They also speak of the three "burning spaces" which serve as a drainage system from the 12 canals into the bladder and for storage of the Yin and Yang principles. According to the ancient Chinese idea, these are two all-important opposing forces.

Everything in the universe, including health, is dependent upon the balance between these forces. They represent male and female, ebb and flow, life and death, wet and dry, sun and moon, heat and cold, strength and weakness. By acupuncture, they profess to relieve tissue obstructions, release "bad secretions" and restore the balance between Yin and Yang that constitutes well-being.

A common sight in the village market-place is the Chinese physician-surgeon with his manikin or chart of vital points. The practitioners seem to have a good combination of courage, dexterity and luck. I have seen them introduce seven or eight needles deep into the tissues without injury to the blood vessels or vital organs. I heard of only a few incidents of broken needles or of fatality following acupuncture.

The needles are of metal: steel, copper, brass, silver or gold. They vary in length from one to two feet. The ends may be arrow-headed, blunt, sharp or spear-headed. The shape is usually round but they vary in thickness. The needles are usually inserted by a blow from a light mallet. The point of insertion, depth of puncture, direction of rotation, number of needles, whether hot or cold, and length of time left in are all varied depending upon the case (and the operator).

Sometimes the needles are left in for a few days. Sometimes heat is applied to the outer end of the needles: hot acupuncture. Rarely are the needles heated before insertion. Sometimes acupuncture is used in conjunction with scarification or moxibution. This last consists in the application of combustible pine cones to the skin.

Strangely enough acupuncture does seem to be an effective remedy. In every village one heard stories of the "miraculous" cures effected by this treatment. It seems of most benefit for various types of rheumatic pains, sprains, etc. Perhaps the beneficial effects are due to counter-irritant action.

The ancient manuscripts prescribe acupuncture for a variety of ailments such as headache, convulsions and fainting spells. When these conditions have an organic basis it is not likely that "remedies" such as acupuncture will be effective.

Acupuncture was introduced into Europe from China by a Dutch surgeon named Ten-Rhyme. Following this the procedure was taken up by quacks who toured Europe and claimed to cure all sorts of diseases by acupuncture. They laid great stress on the absence of any pain except for the initial skin puncture. A later refinement was the use of galvanic currents with the needles, much like our present-day technique for treating warts and naevi. Another modification was the introduction of hollow needles and their use in instilling fluids, drugs and local anaesthetics. Apparently acupuncture has gone a long way since the days of the Yellow Emperor.

* Division of Graduate Medicine, University of Southern California.

MEDICAL PROGRESS:

DICUMAROL

DONALD W. PETIT, M.D., and CLARENCE J. BERNE,* M.D., *Los Angeles*

SINCE the introduction of dicumarol to clinical medicine in 1940 numerous reviews of the subject have appeared.[1,10,26,33-36] These have served to tell the story of the drug and its primary uses. Link has dramatically related the discovery and action of dicumarol[33] and any attempt to detail what is in these reviews would be superfluous. It does seem appropriate, however, to attempt to integrate some experiences of clinicians with dicumarol and to describe some of the broader phases of anticoagulant therapy as they apply to discumarol.

CHEMISTRY AND PHYSIOLOGY

Numerous chemical analogues of dicumarol have been prepared, but none have the potency of the parent substances.[34]

It is certain now that the principal, if not the sole action of dicumarol, in the dosage used clinically, is lowering of plasma prothrombin content. How this takes place is not known. The action is not on formed prothrombin but is accomplished by decreasing the formation of prothrombin. The measurement of prothrombin time has become fairly well standardized, using modifications of Quick's one stage method,[25] although there are still some questions to be answered concerning the proper thromboplastin to use. Brambel feels that he has prepared thromboplastin better suited to clinical use than that now commonly employed;[11] also the question of whether whole or 12.5 per cent plasma is the medium of choice for performance of prothrombin times remains unanswered. Many workers seem to feel that whole plasma is adequate for clinical needs.

Reports appear in which differences in prothrombin time are considered significant without any attempt to show the usual standard deviation for that particular laboratory.[50] The concentration of calcium has been shown to influence the prothrombin of diluted plasma. Certainly the technique of prothrombin determinations demands constant performance by the laboratory worker if uniform results are to be obtained.

While the details of method are a laboratory problem, the mode of reporting results is of prime importance to the practitioner. The last two years have seen vigorous attempts to clarify the confusion surrounding "prothrombin content" and "prothrombin index of activity." Aggeler has collected data from various earlier reports to show the difference in those two terms.[1] Inasmuch as they are both reported as percentage and 50 per cent "prothrombin index of activity" is equal to about 20 per cent by "prothrombin content" (Table 1), it is easy to see how misunderstandings start. Many who are interested in the subject agree that the term "prothrombin index of activity" should be dropped. Aggeler's chart reproduced here reveals the obvious difficulties. A recent article in which the confusion between the two types of expression was evident[18] has been criticized adequately.[22] Every clinician who is going to use dicumarol should know and understand completely the method of reporting used by his laboratory before starting treatment.

Barker et al. felt that all prothrombin times should be reported as percent for normal prothrombin content.[25] They gave their own meticulous detail for the calibration of each batch of thromboplastin with whole and dilute plasma. They felt that a laboratory is not justified in using sets of parallel curves for differing thromboplastins. It is doubtful whether the clinical use of dicumarol demands such exacting methods for reporting prothrombin determinations.

Many laboratories report prothrombin times as such—merely giving the time for the test plasma and the time for normal plasma. This method avoids the

* From the Departments of Medicine and Surgery, University of Southern California, School of Medicine.

TABLE 1.—*Comparison of the Prothrombin Time, Prothrombin Concentration and Prothrombin Index Obtained with Different Specimens of Thromboplastin (from Aggeler, Calif. & West. Med., 64:71-77, Feb., 1946)*

Prothrombin Time in Seconds						Prothrombin Index of Activity				
Specimen					Prothrombin	Specimen				
1*	2†	3‡	4‡	5§	Concentration	1*	2†	3‡	4‡	5§
10	11½	12	19	27	100%	100	100	100	100	100
17½	24	18	27	....	30%	57	49	67	70	....
21	35	21	35	....	20%	48	33	57	54	....
37	75	35	60	60	10%	27	15	34	32	45
97	197	69	118	90	5%	10	6	17	16	30

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† Aggeler, P. M., Lucia, S. P., Unpublished data.
‡ Hurn, M., Barker, N. W., Magath, T. B., Proc. Staff Meet., Mayo Clinic, 19:507, 1944.
§ Davidson, C. S., MacDonald, Am. J. M. Sc., 205:24, 1943.

confusion of percentages and has been utilized by several workers.[41,44,51,55] The evaluation of prothrombin times and concentrations will be given later when the method of dicumarol administration is discussed.

Depression of plasma prothrombin is the most important action of dicumarol; however the drug does influence other blood constituents. Irish and Jacques, working with dogs, demonstrated a depression of plasma fibrinogen when doses of 15-20 mg. per kilo body weight were used.[27] In doses of 3-5 mg. per kilo there was either no effect on fibrinogen level or a slight elevation. These workers felt that this action simulated that of liver toxins. It should be noted that there have been no reports of liver damage from dicumarol as it has been used clinically.

Dicumarol may change platelet stickiness, Wright,[54] and Spooner and Meyer,[52] using an ingenious technique of Wright's, felt that they could show decreased stickiness of platelets in animals treated with dicumarol. This decrease was not correlated with change in platelet count. If true, "*in vivo*," it might explain the ability of dicumarol to lessen thrombus formation in doses that do not affect the venous coagulation time "*in vitro*."

Certain drugs have been found to exert an action that antagonizes dicumarol. The chief of these is vitamin K, particularly the synthetic product menadione bisulfite. This action, at one time denied, is now confirmed and has been thoroughly discussed by Davidson, Freed, and MacDonald.[15] These workers have shown that vitamin K is very effective in shortening a prolonged prothrombin time, but they also believe that the drug may be ineffective when venous coagulation time is prolonged. These results may explain two recent reports of failure of vitamin K to control massive hematuria.[8,49]

Link has written that the methylxanthines exert a clinically significant effect on prothrombin content, tending to raise its level and to antagonize dicumarol.[19,20] Two sets of workers have published their results on the effect of aminophyllin on plasma prothrombin content. Scherf and Schlachmann were satisfied that large doses of aminophyllin shortened plasma prothrombin time.[50] Breytspaak and Greenspan could not confirm this.[12]

Scorbutic animals are more sensitive than normal ones to the action of dicumarol.[35] Thyroid principle does not influence the action of dicumarol.[53] Quinine and perhaps quinidine have a tendency to lower plasma prothrombin content an effect that is overcome by vitamin K.[45] The action of salicylate is parallel to that of dicumarol and there seems no doubt that experimental hemorrhage can be caused by heavy doses of salicylates.[21] The mechanism of this action is not clear but may have something to do with the fact that salicylates have been used as the starting points for the experimental synthesis of dicumarol. Goth submitted a brief note alleging anti-bacterial properties to dicumarol.[23]

The number of reports attesting to the value of dicumarol in thrombo-embolic disease has been large, although the great number of methods now available to treat thrombosis has made it almost impossible to evaluate any one method as compared with the older type of conservative treatment.[2-6,16,29,43,47,56,57] In the last five years, early diagnosis, early rising and postoperative exercises have all played a part in the gratifying reduction in mortality and morbidity from thrombotic disease.

Dicumarol has undoubtedly saved lives, yet experiments upon which the clinical use of dicumarol is based have not reproduced the clinical method of administration of the drug.[17,39,42,48] Thus those workers successful in the treatment of experimental thrombosis used doses of dicumarol that not only lowered plasma prothrombin content but also prolonged venous coagulation time. As Aggeler points out, it has not yet been shown experimentally that dicumarol is effective in preventing thrombosis unless given in large enough doses to alter coagulation time of blood.

Postoperative thrombosis occurs in about 1 per cent of unselected cases.[5] Figures attributing a higher incidence to certain types of operations are hard to evaluate because they generally fail to take age, sex, type of disease process and patient's general condition into consideration.[37] Of cases of deep venous thrombosis, about 20 per cent die of pulmonary embolism if treated without anticoagulants or surgery.[5,29]

Barker has summarized the experience at the Mayo Clinic in the years 1940-1945 with deep and superficial thrombophlebitis and pulmonary emboli.[42] The figures are shown in Table 2.

TABLE 2

Disease and Treatment	Number of Cases	Number of Recurrences	Number of Fatalities
Pulmonary embolus—no dicumarol	687	297	124
Pulmonary embolus—dicumarol given after embolus	180	4	1
Postoperative thrombophlebitis—no dicumarol	897	95	51
Postoperative thrombophlebitis with dicumarol	138	4	0

It is not clear from the report what type of treatment the patients received other than dicumarol.

Reich, Yahr and Egger reported on the use of dicumarol in the treatment of 33 cases of venous thrombosis and nine cases of pulmonary emboli that occurred in 259 general surgical operations.[56] They had no fatalities.

Jorpes' article reported much of his own work as well as that of several other workers using anticoagulant therapy.[29] He quotes G. Bauer as follows:

Disease	Number of Cases	Mortality
Deep venous thrombosis—no anticoagulants	25,628	18%
Deep venous thrombosis with anticoagulant (heparin)	16,495	1.4%

A good and complete review of the use of anticoagulants in thrombo-embolic disease has been written by Zilliacus.[57] His figures compared favorably with those quoted above. In addition he showed a definite reduction in morbidity and thrombotic sequelae when dicumarol was used. Thus, under "conservative" treatment (no anticoagulant and no surgery) thrombosis of calf, or calf and thigh veins required an average period of hospitalization of 35 days with an average of 21 days' fever. Cases treated with dicumarol had an average period of hospitalization of 11 days with an average of eight days' fever.

Zilliacus also commented on the spread of thrombotic processes under conservative and under anticoagulant types of treatment. Thus with conservative treatment, 31 per cent had spread of calf or calf and thigh thrombosis to the other leg. When dicumarol was used, only 2.2 per cent had such a spread.

Zilliacus reported that of 166 patients who survived an initial pulmonary embolus, 63 were treated conservatively and 17 died, 103 were treated with dicumarol and none died. These figures are in close agreement with those of Barker previously quoted.

Jorpes felt that while ligation, exercise, and sympathetic block may produce results comparable to those obtained with anticoagulants, none of these procedures is the final answer and anticoagulants should always be used.[29]

Yahr, Reich and Egger felt that dicumarol is the treatment of choice for thrombophlebitis.[56]

Allen published a preliminary report comparing vein ligation with dicumarol. The doses of dicumarol used were very low by the usual standards.[2] The results as published show no advantage in the use of dicumarol prophylactically inasmuch as of 101 patients who received the drug, three developed postoperative thrombo-embolic complications. In a control group of 562 patients who were of similar age distribution (40 to 64 years), 14 developed thrombo-embolic complications.

The prevention of venous thrombosis by prophylactic dicumarol therapy remains an important phase of therapy not commented upon here for lack of sufficient reports. Reich et al. reported a case of septic cavernous sinus thrombophlebitis cured with sulfonamides, heparin, dicumarol and sedation.

ARTERIAL OCCLUSION

Dicumarol has been used for the treatment of acute arterial occlusions. A recent report advised that heparin and dicumarol be started as soon as a diagnosis of arterial obstruction was made.[7] This was done in the hope of preventing thrombosis in the slowed arterial and venous circulation distal to the obstruction. In a series of 15 patients with acute arterial occlusion who were treated with heparin and dicumarol, three developed gangrene and one died. Of a group of 100 cases of acute arterial occlusion reported in 1935, 50 developed gangrene and 36 died.[38]

The anticoagulant drugs have made embolectomy an operation with a future. If these drugs are started as soon as an arterial occlusion occurs, it is possible that the period of observation prior to embolectomy could be prolonged above the usual six-hour limit.

A report from France recorded the use of dicumarol in the treatment of four young adults with occlusion of the central retinal artery.[14] The author felt that improvement was more complete and rapid than might have been expected with usual therapy.

CORONARY THROMBOSIS

During 1946 three reports appeared with respect to the use of dicumarol in the treatment of coronary thrombosis.[41,44,55] Blumer[9] and more recently Nay and Barnes[40] have emphasized the high incidence of thrombotic and embolic complication of myocardial infarction (from 14 per cent to 37 per cent). It was in the hope of lessening these accidents that dicumarol was used.

Nichol and Page gave dicumarol to 44 patients with myocardial infarction.[41] There was only one instance of pulmonary embolus, and in that case the dose of dicumarol was thought to have been far too low. None of 26 patients treated during the first episode of infarction died. Eight of the entire group of 44 patients died. The average dose of dicumarol was 2100 mg. in a period of 25 days.

Peters et al. treated 110 patients, 50 with dicumarol and 60 received no dicumarol.[44] Of the 60 treated without dicumarol, 13 died, five with pulmonary emboli; of the 50 treated with dicumarol, two died, none with emboli.

Wright gave dicumarol to 76 patients with myocardial infarction; these patients were divided into two groups, complicated (of whom there were 43) and uncomplicated (of whom there were 33).[55] In the complicated group were included those with repeated episodes of multiple thrombi or repeated embolic phenomena. In this group there were 11 deaths (25 per cent) as against an expected 50-60 per cent mortality. In the uncomplicated group there were four deaths (12 per cent) as opposed to an expected 20-30 per cent mortality.

All of the workers felt that adequate controls were lacking in the various series. More reports from other series will be needed before the place of anticoagulant therapy in myocardial infarction can be accurately determined.

Cotlove and Vorzimer wrote that determination of prothrombin time was not an accurate index of clotting tendency in heart disease.[13] In the cardiac patients with thrombo-embolic complications they studied, there was no significant change from normal in plasma prothrombin time.

This should be contrasted with the work of Peters, Guythe, and Brambel[44] who felt that patients with cardiac infarction had an increased clotting tendency which could be detected by serial prothrombin time determinations.

Reese reported 28 failures in the use of dicumarol in 28 patients with multiple sclerosis.[46]

ADMINISTRATION OF DICUMAROL

Although dicumarol is absorbed rapidly from the intestine, its effect is not noticed before 18 hours and

rarely may be delayed 48 to 72 hours. This lag period should be remembered when an emergency anticoagulant is needed as in arterial occlusion or pulmonary embolism.

Attempts to form a dosage schedule for dicumarol based on patient weight have been unsuccessful. The individual response is not uniform and the only safe way to be guided in dosage is by changes of prothrombin time. All other criteria for proper dosage such as hematuria or capillary coagulation time seem dangerous or unreliable.

The average initial 24-hour dose of dicumarol is 300 mg. given at one time, followed by 200 mg. in the next 24 hours, if the patient is not small. Daily prothrombin times are performed, and maintenance dosage depends on those determinations. If the reports from the laboratory are returned in terms of prothrombin content as per cent of normal then the aim is to keep prothrombin content around 20 per cent of normal. If the content is above 20 per cent of normal, give 100 mg. of dicumarol. On those days when the content is below 20 per cent of normal, omit dicumarol.

Many feel that a satisfactory aim of treatment is to double the whole plasma normal prothrombin time or to treble the normal prothrombin time of 12.5 per cent plasma. Wright tried to keep the prothrombin time of his cardiac patients between 30-35 seconds.[55] He gave 300 mg. of dicumarol initially and daily until the prothrombin time reached 35 seconds. At this point dicumarol was stopped. It was readministered in doses of 100 mg. when the prothrombin time fell below 30 seconds.

Nichol and Page tried to keep the prothrombin time between 27 and 35 seconds by similar adjustment of dosage.[41]

All schemes of dosage rely upon frequent determinations of prothrombin time.

INDICATIONS

Barker has listed the indications for dicumarol administration;[4] to the usual thrombo-embolic diseases will probably be added myocardial infarction and acute arterial occlusion. Jorpes emphasized that pulmonary embolus and arterial occlusion are emergency states and should receive initial administration of heparin with dicumarol.[29] The value of anticoagulants in cardiac arrhythmias is a problem whose answer is awaited eagerly.

CONTRAINDICATIONS

The contraindications to dicumarol have not been changed appreciably from Barker's list:[4]

1. Presence of definite renal insufficiency.
2. Presence of definite hepatic insufficiency.
3. Hepatogenous jaundice particularly if associated with prothrombin deficiency.
4. Subacute bacterial endocarditis.
5. Purpura or any other blood dyscrasia with a tendency to bleed.
6. Recent brain or spinal cord surgery, injury or hemorrhage.

Conditions in which the drug must be used cautiously are:

1. Ulceration, or easily bleeding lesions.
2. Vomiting due to gastric or intestinal obstruction.
3. Continuous or repeated gastric or intestinal drainage.
4. Dietary or nutritional deficiency.

TOXICITY

The toxic reaction to dicumarol is hemorrhage. Aggeler, in his review quoted a general incidence of this complication of 8 per cent, with five deaths due to hemorrhage in 1,471 patients treated with dicumarol.[1] Barker wrote that the seriousness of dicumarol bleeding had been overemphasized.[5]

There were two reports of massive hematuria due to dicumarol that failed to respond to vitamin K.[8,49] One case and a lengthening of prothrombin time from 190 seconds to 240 seconds after 120 mg. of menadione bisulphite was given intravenously. In such cases fresh transfusion of citrated blood are needed. Both cases took larger doses of dicumarol than thought proper now; one man took an average of 300 mg. daily for seven days; the other man took 100 mg. daily at home, for 17 days. If such dangerous sequelae are to be prevented, dicumarol administration must be governed by frequent determinations of prothrombin time.

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California Cancer Commission Studies*
Chapters II and III

Principles in the Treatment of Cancer

EMILE HOLMAN, M.D., *San Francisco*

THE physician who first examines a patient with presumed or suspected cancer must be aware of the potentially fatal damage his examination may inflict, since he may by this very examination nullify completely all subsequent efforts to cure. I refer to the need for extreme gentleness in handling any malignant tumor lest by squeezing or compressing it, tumor cells are forced into lymphatic or blood channels and thence into regional lymphnodes or lung.

For the same reason multiple examinations should be avoided. Microscopic studies of malignant tumors frequently reveal invasion of blood vessels and lymphatic channels by malignant cells which then lie on the brink of a swiftly moving stream capable of carrying them into inaccessible areas. It is probably true that many cancerous patients are already doomed before they are examined by a doctor because of the mistaken belief that massage and hot applications are good treatment for a lump. Occasionally it happens that the doctor may not think of cancer as applying to a particular case and may unwittingly prescribe such dangerous treatment.

Of equal importance at the first examination is recognition of the urgency of *immediate* treatment of a possibly malignant tumor—not in two or four or six weeks, but *now!* Invasion of a circulatory channel by malignant cells and migration to remote areas may occur at any time, and as a result the surgical care of cancer should be instituted as soon after discovery as possible. It may be justly said that operation for cancer is almost as much an emergency as operation for a ruptured ulcer or gangrenous appendix.

A third all important principle in cancer therapy is never to postpone the institution of surgical care simply because no signs of malignancy have appeared. For example, a single newly developed lump in a woman's breast, no matter how innocent it appears, or how symptomless it may be, must be considered as subject to immediate removal for macroscopic and microscopic study. Under no circumstances should such a lesion be *watched* for the signs of malignancy to appear, such as dimpling of the skin, retraction of the nipple, distortion or fixation of the breast, or palpable lymphnodes. When these signs are present it is usually too late for cure. The ideal time to cure a cancer is when it is impossible to recognize it clinically as cancer, when the only symptom is nothing more than a lump, as in the breast, or a single bleeding ulcer, as in the large bowel, or a scab on the lip that does not heal, or a gastric ulcer refractory to treatment, or a persistent hacking cough as in cancer of the lung, or persistent hoarseness as in cancer of the larynx, or mild difficulty in swallowing as in esophageal cancer, or the sudden appearance of itching or scabbing of a black mole.

A fourth important principle in cancer therapy is not to neglect *seemingly* unimportant symptoms without *proving* them unimportant. When a patient complains of bleeding from the bowel it must not be ascribed to hemorrhoids *without* a digital and proctoscopic examination, and if these are negative, without a barium enema examination. These should follow each other in that order in every instance of bleeding from the bowel. Similarly, a change in cough habit, and particularly a persistently blood tinged sputum, demands without fail an immediate roentgenographic examination of the lungs. Bleeding from the vagina must not be ascribed to simple myomata without proving it by careful vaginal examination and miscroscopic section of uterine scrapings whenever indicated.

All too frequently patients present themselves with inoperable cancer and a history that gives damning evidence of a doctor's neglect of early symptoms and of his failure to do simple examinations when these symptoms first sent the patient to the doctor for advice. They received improper advice because important examinations were neglected.

A fifth all important principle in cancer therapy is not to undertake an operation for a presumed simple or innocent looking lump or lesion without having access to frozen section diagnosis—not tomorrow and not in another city a few hundreds miles away, but immediately and locally! Delay in performing the more radical operation for complete removal of the local lesion may result in ultimate failure and an avoidable death from cancer. This is because the excision of a mass on an assumption that the tumor is benign frequently leads to incomplete local removal and to transection of lymphatics

* Organized by the Editorial Committee of the California Cancer Commission.

filled with cancer. For the same reasons no doctor should remove any lump unless he is qualified to perform a radical operation at once if indicated.

As to the principles underlying the surgical excision of the lesion itself, there is only one: *complete* removal—wide excision of the local tumor and dissection of draining lymphnodes "en bloc" whenever possible. More specific surgical measures will be presented in the chapters dealing with specific lesions.

GENERAL PRINCIPLES

1. Be gentle in examination of a tumor—it may be cancer.
2. Cancer is an emergency.
3. Don't *watch* lumps or ulcers.
4. Be thorough—run down every sign and symptom.
5. The first sign of cancer may be a common symptom.
6. Don't tackle more than you can handle.

Examination of the Patient for Cancer

Chapter III

OTTO H. PFLUEGER, M.D., *San Francisco*

"*EARLY Cancer is Curable.*" This implies early diagnosis and adequate treatment.

We are here concerned with early diagnosis. It is a fact that a careful history and physical examination will go far in reducing cancer mortality. For this reason we devote this section to what may appear so simple a thing as discussion of the examination of a patient. It is a fact that we have been culpable in neglecting the performance of this basic procedure. Our shortcomings are frequently due to carelessness or laziness. Hemorrhoids are removed for rectal bleeding without finger examination—breasts are not carefully palpated—vaginal examinations not made. *The basis of all diagnosis is the history and physical examination.* This cannot be overemphasized. These guide us in determining the need for further investigation.

There is much education of the public concerning cancer. As physicians we must keep cancer in mind as a possible diagnosis. We must do the simple procedures. Remember a "psychoneurotic" individual can get cancer just as well as a phlegmatic, well-balanced one. The individual who visits a physician for an examination because of the fear of cancer is an intelligent person. Such a person is entitled to a complete and thorough examination. All too frequently, when the doctor ascertains there are no symptoms, he says no examination is necessary. This is a deplorable attitude and defeats the purpose of all cancer education.

Patients may come to the doctor for examination with or without symptoms. The latter probably require even more careful investigation. Cancer is an insidious disease—there is *no symptom complex* for early cancer. It is noted for its paucity of symptoms. Nature, unfortunately, is uncooperative. An unseen and nonpalpable tumor makes its presence known when it interferes with the function of the organ involved, or when it is extensive enough to become necrotic and bleed, or encroach upon neighboring nerves and produce pain.

What, then, is our course of procedure? Remember, we are interested in curing cancer, in being able to eradicate it completely while it is still a local disease or at the worst confined to its neighboring nodes.

HISTORY

Elicit a Careful History. This should include family history, past history, and present illness (symptomatology), if there be any. If an orderly procedure is followed, one is less liable to overlook pertinent points.

Family History:

In a general way we may say cancer is not hereditary as far as we know, yet the susceptibility is greater in offspring where cancer has been present in the antecedents. Certain diseases are definitely familial and precancerous, such as congenital polyposis of the colon. Get a family history —it may give a valuable lead. Those who have a familial incidence should be reassured by being told they are fortunate in being aware of their susceptibility and that they can avoid future trouble by frequent examinations.

Past History:

Occupation may be an important guide. There are a number of carcinogenic agents used in industrial activities, *e.g.* coal tar and coal tar derivative and aniline dye products. Frequent x-ray exposures may produce skin changes, as does also excessive exposure to actinic rays and other irritating factors, *e.g.* cancer of the lower lip in farmers and seamen.

It is important to know about those conditions which may produce a stomatitis and glossitis of a chronic nature. We refer to chronic irritation from ill fitting dentures, excessive tobacco, syphilis, and untreated avitaminosis. Chronic oral mucous membrane changes are common where these factors are encountered.

Present Illness (Symptomatology):

As stated above, the onset of cancer is insidious. While the symptomatology may be vague and indefinite, attention to minute complaints is important. *Any change in the function of a system merits attention*—the onset of a chronic cough, voice change, a change in bowel habit (as unsual constipation, tenesmus or diarrhea), loss of appetite, any change in one's feeling of well-being. Any discharge, especially a bloody one, from a body orifice may be most important and merits immediate attention.

Take an orderly system history. Inquiry concerning symptoms may elicit information which the patient considers too insignificant to mention.

An individual may complain of a sore or a lump. One must know all about that. How long has it been present? Has it grown—if so, slowly or rapidly? If a mole, has the color changed? If a sore, how did it start? What was the apparent inciting factor? Was there a lump present before the sore started? There are so many things one can know about a sore or lump which are important. Find them out!

Pain is not an early symptom, except in one condition. The presence of pain in young individuals is probably the earliest symptom of a bone sarcoma. Attention to this fact with careful investigation from the radiologic standpoint will go far in discovering a bone tumor in an earlier stage. Too often such a complaint is passed off without x-ray examination, as a "growing pain" or neuralgia, and a correct diagnosis is not made until a tumor is palpable. A roentgenogram will show bone changes before a palpable lump is present.

In general, however, *pain is a late symptom in cancer*. We must make the diagnosis before pain occurs, on the basis of other minute or vague complaints. Consider the diagnosis of cancer before pain is present.

Fatigue, loss of weight, or related physical findings as anemia, pallor, poor tissue turgor, jaundice, etc., are symptoms more or less common to cancer in various locations. They are manifested usually late in the course of the disease and hence are of little value in making an early diagnosis. Don't wait for any of these signs or symptoms before considering a diagnosis of cancer.

PHYSICAL EXAMINATION

How to make a physical examination? The answer is simple—*make a thorough complete physical examination, inspecting all the body orifices.* We shall consider points to think about in doing so.

Skin and Subcutaneous Tissue:

Observe and palpate for lumps or moles. Is it a single one or are there more than one? Are there areas of pigmentation? If a mole is present, is it in an area where it can be irritated by trauma or constant rubbing? Especially in people who are out of doors a great deal, examine the face and hands for scaling and keratosis.

Oral Cavity:

Examine it thoroughly with a good light and mirror. Look not only for an ulcer, but for those conditions which signify chronic changes and may be precancerous. Observe for leukoplakia, chronic glossitis, stomatitis, or evidence of an ill-fitting denture. Attention to these goes far in the avoidance of future cancer. Palpate as well as inspect.

Lymph Nodes:

Unfortunately, lymph nodes enlarged because of cancer mean that there already has been a spread of cancer from the point of origin and the disease is no longer entirely local. Such cases are by no means hopeless, for the primary and secondary disease in many instances may yet be eradicated and a fair percentage of five-year cures obtained.

Cancer spreads generally along fairly well defined lymphatic routes so that the presence of nodes in any given area will indicate the probable location of the primary tumor.

Neck:

Lip cancer first spreads to the suprahyoid area as a rule, as does cancer of the buccal mucosa, anterior two-thirds of the tongue, floor of the mouth and gums. Tonsil, nasopharynx and lower pharynx tumors usually metastasize to the deep cervical nodes. A necessary point to remember is that in a fair percentage of cases the first sign or symptom of a cancer in one of these areas, especially in the last three locations, is a lump in the neck, *i.e.* a metastasis. *The commonest cause of asymmetrical lymphadenopathy in the neck of an older individual is metastatic cancer.* A person presenting this sign must have a thorough examination of the mouth, nasal passages and entire pharynx. The primary tumor may be so small that repeated examinations may have to be done before it is found. Only after initial thorough examination should a biopsy of neck nodes be done.

Supraclavicular involvement may be from the breasts or thorax. The signal node on the left may be involved as a result of tumor in the abdomen or even testicle.

Axillary nodes signify a tumor of the breast, upper extremity, upper back or anterior chest wall. Examine for axillary nodes with the patient's hand resting on the examiner's shoulder.

Inguinal nodes are involved by spread from the external genitalia, lower trunk, extremity or from the anal region. This last area is sometimes forgotten—remember to examine the anal area when enlarged inguinal nodes are present.

Breasts:

Examine the breasts of all women. Look for changes in configuration, appearance of nipples and skin, but most of all for a lump. The time to diagnose cancer of the breast is when there is only a lump present; in other words, when the diagnosis is clinically doubtful. Note whether there is only a single lump or more than one lump present. Ob-

serve its consistency, movability and delineation of the border for roundness or nodularity, for these suggest the nature of the tumor. We pass these over lightly for they will be discussed in the supplement on breast tumors. Examine the breasts with the patient sitting; also lying with the arms at the sides and above the head. Have the patient also sit forward so the breast, if pendulous, may be palpated between the two hands. Above all, palpate carefully and gently.

ALWAYS DO A PELVIC EXAMINATION

Pelvic Examination:

Bimanual palpation and inspection in good light are most important. Look for discharge, its nature if present, erosion, ulceration, and easy bleeding on touching the cervix.

Rectum:

A high percentage of rectal cancers can be palpated with the examining finger. This simple procedure is too often overlooked. Completely unsuspected rectal cancer has been found by finger examination when there were no symptoms to suggest the need for such an examination. A proctoscopic examination is also indicated because many cancers which cannot be reached by the finger can be seen. The prostate should also be palpated.

Blood and *Urine* examinations should be routine. Roentgen examination of the chest and gastrointestinal tract are advisable, especially in individuals over forty.

The foundation of the diagnosis is the history and physical examination. We can give assurance of the probable absence of a lesion only if we have performed the necessary examinations.

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EDITORIALS

Sulfonamide Therapy of Intestinal Disorders

With the discovery of the bacteriostatic action of sulfonamide preparations on a host of gram negative bacilli, a bright new vista opened up in the management of intestinal tract infections. There seemed to be great promise, not alone of successfully treating specific infectious diseases, but also of carrying out successful prophylactic therapy to prevent secondary complicating bacterial invasion, particularly in surgical conditions. At present the hope that certain intestinal infections may be completely eliminated by chemotherapy has in fact been justified, so that it is important to take stock of the effectiveness and the limitations of the sulfonamide drugs which are now most widely used.

The drugs to be considered may be logically divided into two distinct groups. The first group is composed of those preparations which are poorly absorbed from the gastro-intestinal tract and consequently exert their chemotherapeutic effect purely by local action within the intestinal lumen. The second group is composed of a more widely used series of preparations which are readily absorbed from the intestinal canal and exert their therapeutic action not only within the intestinal lumen, but also diffusely through all tissue structures, including the intestinal mucosa and submucosa. In the first group three preparations in particular have been given extensive clinical trial. These are sulfaguanidine, sulfasuccidine (sulfanil sulfathiazole) and sulfathalidine. The first two were used throughout the world in the practice of military medicine to combat a wide variety of intestinal infections during the recent war. Because of this extensive experience reported upon by a large number of observers, a summary of their effectiveness now seems conclusive. The therapeutic results with the third and more recently developed preparation, sulfathalidine, do not warrant a decision at present that it is superior to the other two. Of the many preparations in the second group of readily absorbable sulfa compounds, only two need to be considered in reference to intestinal infections—sulfathiazole and sulfadiazine. The first of these two is included only because it was developed at the onset of the recent war and physicians gained a broad experience with it before the second, sulfadiazine, came into general use. Of the two, sulfadiazine receives preference largely because it is less toxic than sulfathiazole.

In choosing which type of sulfa drug to use in treating an intestinal infection or in attempting to combat a possible spread of infection from the intestinal canal, the decision not only depends upon the effectiveness of a given preparation, but also on the degree of toxicity which it may cause. Originally the less absorbable type of preparations included in group one were developed because their toxicity was negligible, despite their administration in large doses, in comparison to the earlier sulfa compounds, some of which produced a high incidence of toxic effect. Their poor absorption resulting in low toxicity, together with their therapeutic effectiveness in dysentery bacillus infections, has placed them in a position of high therapeutic importance in combating intestinal tract disease. However, with the development of sulfadiazine which has a low degree of toxicity despite its ready absorption from the intestinal lumen, it appears that this preparation is the therapeutic agent of choice among the sulfa compounds in the management of digestive tract infections. It also has the advantage of being effective in relatively small dosage and consequently it is less expensive than the less soluble compounds.

The management of bacterial infections of the intestinal tract by sulfonamide therapy may be divided into three major categories. The first and most clear-

cut problem is the treatment of specific bacillary infections, such as those caused by the shigella and salmonella groups of organisms. The second problem of management is infection in the gastro-intestinal tract of unknown etiology, such as occurs in certain cases of chronic diarrhea and ulcerative colitis. In these conditions the results of sulfonamide therapy can only be judged by its influence on the clinical course of the disease. The third problem is one of prophylactic therapy directed against the spread of the colon bacillus outside of the intestinal lumen which may occur in cases of intestinal perforation or following surgical procedures on the small intestine and colon. The results of this type of therapy can only be judged after statistical analysis of a large number of similar cases.

The therapeutic results in those forms of dysentery where the infection has been due to the shigella group of bacilli have been almost uniformly good. Not only can the etiological agent be eradicated in both acute and chronic infections and in the carrier state, but in the acute cases the time of disability is materially shortened. If infection is due to the Sonne form of dysentery bacillus, a favorable response may not be encountered as the organism is occasionally sulfa-resistant. The salmonella group of bacilli responds poorly to chemotherapy with the sulfonamide preparations; in fact, most types of typhoid and paratyphoid infection are completely resistant. The proteus group of bacilli, which may be considered as causative agents in the production of diarrhea at times, is usually susceptible to sulfa therapy, but certain strains may remain completely resistant. The cholera bacillus has not proven susceptible. To secure a favorable effect from the treatment of any of these intestinal infections it is essential that adequate amounts of the sulfonamide drug selected be given for seven to ten days. If no beneficial effect has occurred in this length of time, none may be expected with further treatment. In cases of therapeutic failure, changing the form of the sulfa preparation in order to carry out further treatment will not prove successful. In cases of relapse, retreatment is occasionally rewarded with success.

The use of sulfonamide medication in cases of diarrhea from which no causative organism has been recovered from the stool is often rewarded with success and should be tried. Doubtless the majority of the cases of this type which responded to therapy are primarily bacillary in origin. This same form of medication has been popular in the management of ulcerative colitis and as each new form of sulfa preparation makes its appearance and is tried in the treatment of this disease, elaborate claims are made as to its beneficial effects. Gradually it has become apparent that the sulfa drugs do not cure this disease and rarely produce any lasting benefit. Symptomatically some patients improve and occasionally the mucosal ulcerations show a tendency to heal, due to a reduction in the bacterial flora present in the bowel which are apparently causing a systemic reaction to infection. Consequently these drugs should be tried in selected cases exhibiting evidence of chronic infection. They may be given for long periods of time without producing harmful effects.

The oral and intravenous administration of sulfathiazole and sulfadiazine in the management of perforating cases of appendicitis is now an established procedure and has materially reduced the mortality and the incidence of complications in this common disease. Active inflammation of the appendix may be curtailed and threatened perforation may be prevented. When perforation into the peritoneal cavity has developed, this drug therapy will aid in the localization and walling off of the inflammatory process and in the prevention of diffuse peritonitis. Similar beneficial effects may be obtained from sulfa therapy in other types of intestinal perforation, such as from a duodenal ulcer or from a diverticulum of the colon. Statistics show that the prophylactic use of sulfonamide drugs as a preliminary procedure in preparing the bowel for surgery, particularly the colon, has tended to reduce the operative mortality and also the incidence of postoperative complications which are of an infectious nature. The use of these drugs for this purpose is now a standard surgical procedure. However, the indiscriminate introduction of sulfa compounds into abdominal wounds has now been largely abandoned.

CLINICAL CONFERENCE

The Neurology of Alcoholism

EPHRAIM ROSEMAN,* M.D., AND CHARLES D. ARING,* M.D.: According to Dr. Roger Lee,[11] "It is an old saying that alcohol is a highly inflammable substance whether you apply a match or a word to it." Through the ages alcohol has been used to allay fear and insecurity, to neutralize frustration, for emotional release, and as a social catalyst and aphrodisiac. Alcoholism evolves from numerous factors, including, to be sure, idealization of drinking in tradition, custom, and mores. In what follows we will attempt to summarize briefly the more important neurological complications as we know them today that are associated with acute and chronic alcoholism.

Alcoholism in Differential Diagnosis of Coma

Alcohol is a common cause of coma in admissions to a general hospital. In a study of patients admitted in coma to the Boston City Hospital,[5] alcohol was responsible in 59.1 per cent of 1,167 cases. It is well to know that 2 per cent of patients admitted in alcoholic coma die.

Alcohol and Trauma

Coma may of course be precipitated by an injury to the head of an inebriated individual; it is common for subdural bleeding to occur in association with alcoholism. Bleeding beneath the dura usually follows shearing off of certain of the bridging veins which extend from the dura to the venous sinuses. Alcoholics obviously have a propensity for trauma; however, some investigators[3] have determined that the vitamin content of the blood, including vitamin C, is lowered in the patient addicted to alcohol. Chronic abuse of alcohol may possibly lower the threshold to extravasation of blood. In relation to this point it may be mentioned that scorbutic children suffer subdural hemorrhage, as well as hemorrhage of other types on slight trauma.[10] It is suggested that there may be a mechanism common both to the alcoholic and scorbutic which may dispose toward the production of certain neurologic complications of the hemorrhagic variety.

Medico-Legal Aspects of Drunkenness

In the wake of the strong desire for quantitation and standardization that has for long affected medicine, there has been a tendency to treat the alcohol content of the blood as a sort of slide-rule in the diagnosis of drunkenness. It has been thought by some that the level of blood alcohol could be equated with clinical intoxication. There are two main fallacies with this notion: As yet there is no thoroughly reliable method for determining the blood alcohol, and, regardless of the reliability of method, bemusement with the blood alcohol usually is not associated with respect for the adaptative capacity of the central nervous system.

The phenomenon of adaptation occurs not only to alcohol but also to other substances—for example, sedatives and analgesics. The question of adaptation of the central nervous system to alcohol is a complex one, which has been thoroughly considered both experimentally and clinically in the studies of Mirsky, Piker, Rosenbaum, and Lederer.[17] It has been known for years that the symptoms of alcohol-

* From the Division of Neurology, University of California Medical School, San Francisco.

TABLE 1.—*Causes of Coma as a Presenting Sign and Their Mortality. (From Solomon and Aring, 1935)*

Disease	Number of Cases	Per Cent Total Comas	Per Cent Non-alcoholic Comas	Cases of Group Ending Fatally	Per Cent of Group Ending Fatally
Alcohol	690	59.1	.....	14	2.0
Trauma	152	13.0	32.0	48	31.5
Cerebral vascular lesions	118	10.1	24.7	91	77.1
Poisoning	33	2.8	7.0	3	9.0
Epilepsy	28	2.4	6.0	0	0.0
Diabetes	20	1.7	4.2	11	55.0
Meningitis	20	1.7	4.2	20	100.0
Pneumonia	20	1.7	4.2	18	90.0
Cardiac decompensation	17	1.4	3.5	12	70.6
Exsanguination	10	0.9	2.1	10	100.0
Central nervous system syphilis	7	0.6	1.4	0	0
Uremia	7	0.6	1.4	7	100.0
Eclampsia	7	0.6	1.4	3	42.8
Miscellaneous	38	3.2	8.0	26	68.4
Total	1167	100.0	100.0	263	22.5%

ism are most obtrusive with a rising blood alcohol than when it is falling. Sometimes it is forgotten that different people respond variously to identical blood alcohol concentrations; such factors as environment, both external and internal, emotional disturbances, the form in which alcohol is ingested, as well as the phenomenon of adaptation are all considerations.

Mirsky and his co-workers used hepatectomized and normal rabbits in their experimental studies of the adaptability of the central nervous system to alcohol. It was found that when the concentration of blood alcohol was raised very slowly, relatively high blood levels were obtained without the development of the signs and symptoms of intoxication. Adjustment may be made by the central nervous system to high concentrations of alcohol if adequate time is permitted for compensations to occur.

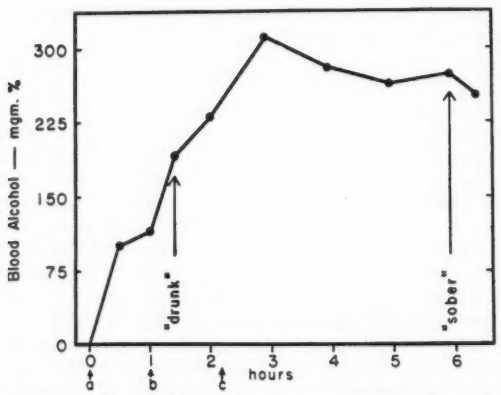

Fig. 1.—The blood alcohol concentration consequent to drinking at (a) 1.0 gm. per kg., (b) 0.25 gm. per kg., and (c) 0.25 gm. per kg. The point at which the patient revealed the signs and symptoms of alcoholic intoxication, and the point at which the patient subsequently became sober, are depicted by arrows. (From Mirsky, Piker, Rosenbaum, and Lederer, 1941.)

Studies in man yielded comparable results. Figure 1 illustrates that the subject became "drunk" at a blood alcohol level of 200 mg. per cent within a period of less than two hours after initiating measured drinking. Drunkenness occurred with a rising blood alcohol. However, at the end of the six hours when it was determined by clinical criteria that the patient was "sober," the blood alcohol level had risen further to approximately 260 mg. per cent. This experiment may be repeated with analogous results in various persons or in the same person. The administration of metrazol may profoundly stimulate the central nervous system and restore function to some degree, at even higher concentrations of blood alcohol than is possible otherwise.

Mirsky, Piker, Rosenbaum, and Lederer summarized their studies as follows: "It is apparent that, given a blood alcohol of 200 mg. per cent or higher, the only deduction that is permissible is that the subject may have been drunk at some time up to the moment the blood sample was drawn, and not necessarily that the subject was drunk at that moment, since the quantity of alcohol at any given time does not serve as a fixed and specific indication of the presence of symptoms."

It has been demonstrated quite clearly that the level of blood alcohol may not be equated with the diagnosis of intoxication. As is usually the case the organism striving to maintain homeostasis is difficult of quantitation; and, as always, it takes a man and not a machine to understand mankind.

Psychodynamic Aspects of Alcoholism

Many studies have been made of the personality of the alcoholic, which in most features resembles that pertaining in other types of addiction. A fundamental difference between the normal and the addict is that the latter demands more than physical satisfaction from the substance to which he is addicted; in addition he requires security and the assurance of self-assertion. The addict is an impulsive, he sacrifices the future for the present instead of the other way around; he must have what he desires immediately and there is no resisting the urge. Kleptomania is an analogous type of impulsive behavior, and may be thought of as theft addiction. Food addiction is in the same category; food is devoured impulsively in the attempt to get something more than the physical satisfaction from it. Persons addicted to drugs are of the same order, but here there is the complication of the added chemical effect; the need for increasing doses of a drug has a physiological basis as well as a psychological one. As long as a drug remains protective, it is not an addiction; for the addict the drug has a subtle, imperative meaning. In him dependence becomes so overwhelming as to nullify all other interests.

The problem of addiction may be found in the nature of the gratification sought, the need to satisfy certain infantile longings especially for security and for the maintenance of self-esteem simultaneously, for which the normal has developed a more mature technique than that of taking something in the mouth or subcutaneously. The reasons addicts act in the manner that they do may be found in the story of their psychological development. The origin and the nature of addiction are not determined by the chemical effect of the drug but by the psychological structure of the patient. Possibly the most readily obvious proof of this is the fact that persons may become addicted to completely inert substances such as placebos.[6]

So it may be said that addicts are those for whom the drug or whatever it may be has a special significance. For them it means the hope of fulfillment of deep, subconscious desires, more urgently felt by them than are the sexual or other instinctive longings by the normal personality. Parenthetically, adult sexuality is rather disorganized in the addict. Extraordinary regression occurs and we see the manifestations of many of the stages of infantile sexuality (oedipus and masturbation conflicts, and especially pregenital impulses).

The relationship between addiction and manic-depressive states is quite clear. The period of elation

obtained with a drug may be looked on as an artificial mania. In the final stages of addiction the patient lives in goalless, alternating states of elation and "morning after" depression, corresponding to the alternation of hunger and satiation in the mentally still undifferentiated infant. There occurs an increasing insufficiency of the elation achieved so that larger and larger quantities of drug become necessary at shorter and shorter intervals. As the periods of elation become shorter, the depression becomes more nearly permanent.

The use of alcohol is characterized by the fact that inhibitions are removed from consciousness before the instinctual impulses (in vino veritas). A measure of relief is obtained by the ingestion of alcohol, particularly if the internal censor is a very strict one. This part of the personality, sometimes termed the superego, has been defined as that part of the mind soluble in alcohol. Alcohol has been extolled for its power to banish care: barriers and obstacles seem insignificant, and gratification near. The reason for reverting to alcohol is the existence of external frustrations or internal inhibitions, and among the latter, depressive inclinations are of the greatest importance. When the misery is at an end, the drinking may or may not be halted. If it is not, such persons are termed alcoholics. They partake of the personality that has been described for addicts in general. In therapy directed toward cure the external frustration or internal inhibition first must be determined, and the patient made aware of its existence and the reason for his specific reaction thereunto.

Several characteristics are rather specific for alcoholism. It has been shown that the person addicted to alcohol has been exposed to difficult family relationships that created frustrations in childhood. These frustrations occur especially during the oral stage of infantile psychosexual development —the earliest stage of development, when the mentally undifferentiated infant obtains most of his gratification by mouth. If he does not receive this normal gratification, his attention will be fixated on the mouth area, and what is termed an oral fixation is developed. In boys who are the anlage of most adult alcoholics, the person who does the frustrating quite naturally is the mother, and the baby turns away from her to the other parent for gratification. All thoroughgoing investigations of the psychology of alcoholism reveal not only typical oral traits but also homosexual ones. It is only necessary to call to mind the numerous drinking customs to confirm this fact. That latent homosexuals, seduced by social frustrations, are fond of alcohol is more probable than that alcohol through its toxic effects is conducive to homosexuality.

In the effort directed toward therapy of the person addicted to alcohol, the psychodynamic principle that the earlier the fixation the more difficult the cure, must be borne in mind. Oral fixation develops early and the chances are good that the process therefore may have become relatively irreversible. It must be determined whether the person resorts to alcohol from external or internal distress, and whether or not he leaves off when he ceases to need it for this purpose.

Periodic drinking is constructed along the same lines as the periodicity of the manic-depressive states. Whereas alcohol helps get rid of depressive moods that return in the after effects, in some persons drinking may immediately precipitate depressions.

Pathogenesis of the Neurological Aspects of Alcoholism

In a consideration of the pathogenic mechanism of the neurological sequelae of alcoholism, stress will be laid on the complications resulting from chronic ingestion. In the past it was considered that alcohol had a direct toxic action upon the nervous system. The trend at present is away from implicating a toxic factor in the production of neurologic deficits. Evidence from both the laboratory and clinic seems to favor the idea that many of the chronic neurologic deficits to be described may be reproduced by a diet prolongedly deficient in vitamins, without the ingestion of alcohol. In other words, neurological sequelae are initiated by some chronic metabolic, specifically avitaminotic disturbance. There is evidence that alcohol in a nutritionally deficient subject will cause marked exacerbation in pathological and clinical pictures, or even hasten their inauguration. It has been noted that alcoholic avitaminosis may be due to several factors: (1) Neglect of diet by persons chronically addicted to alcohol; (2) Interference with absorption of vitamins, owing to gastritis or diarrhea and other intestinal changes associated with alcohol ingestion; (3) A normally balanced diet may be rendered inadequate for the alcoholic person even in the presence of normal resorptive function by increased vitamin requirement needed to cover the increased caloric intake; (4) Increased sweating may assist in the depletion of water soluble vitamins; and (5) Alcoholics are prone to infections which have an inhibitory power on vitamins.

Physiopathology of Alcoholism

The physiologic effects of alcohol may be divided into the acute and chronic phases. The ingestion of alcohol causes a rapid dilatation of the vascular bed, including that of the brain, and it is this latter action which to a great extent is the basis for its therapeutic use. The statement, "that the drug affords comfort to the patient should alone suffice as a reason for its use, provided, of course, that it does no harm,"[7] would seem adequately to sum up the therapeutic value of alcohol. Further, as Rolleston[19] states, ". . . it may soothe the last lap of life's troublous transits." If alcohol is taken in excess, the vasodilatation of the cerebral vascular bed may become extreme and lead to stasis, serous transudation, and perivascular hemorrhage.

The brain in cases of acute alcoholism in which the patient survives for less than a day is not very striking. Grossly there is usually hyperemia, espe-

cially of the cortical gray matter, sometimes associated with edema and flattening of the convolutions. In those patients who survive for more than one day, the morbid anatomy may easily escape attention and at most one sees slight perivascular histiocytic infiltration, especially along the small and middle-sized pre-capillary blood vessels of the medulla oblongata. It is important to note that the pathologic changes associated with acute alcoholic intoxication are not specific and may be found in other types of poisoning. The best evidence as to whether or not alcohol is implicated in causing death is the chemical analysis of the brain tissue for alcoholic content.

Alexander [1] has noted that the cause of death in chronic alcoholism is related to (1) trauma, so frequently associated with chronic alcoholism; (2) intercurrent infection, and (3) chronic diseases of the central nervous system which develop from five to forty-five years after the continuous and excessive use of alcohol. The question of trauma has been discussed already in relation to subdural hematoma. It is probable that the incidence of subdural hematoma is more common among alcoholics than in relation to any other single factor. The occurrence of intercurrent infection, such as pneumonia or subcutaneous abscess, is quite high in those chronically addicted to alcohol. It has been shown that the death rate of pneumonia is proportionately higher in alcoholics than in patients having any other classification of disease. Cause of death is frequently attributed to diseases of the nervous system without such exogenous factors as trauma or infection. The pathological picture in this latter group is more or less the same; variations in the clinical picture are due to the fact that the effects may be more marked in one portion of the neuraxis than in another.

There are two main pathological syndromes associated with the disorders of the nervous system in chronic alcoholism. One is the ectodermal involvement described by Adolf Meyer,[16] Greenfield,[9] Alexander,[1] and others, in which changes occur predominantly in the frontal cortex of the brain and the motor cells of the spinal cord. There is an associated degeneration of nerve fibers, predominantly affecting the myelin sheaths. Although these changes may be found in persons suffering from nutritional diseases, such as beriberi or pellagra, it would seem that alcohol invariably produces a much more severe picture so that frequently there occurs associated involvement of the axis cylinders.

The second pathological syndrome is that involving primarily the vascular elements of the central nervous system. Usually it is found in association with a more acute or subacute deprivation. It is characterized by mesodermal proliferation and varicose deformities of the smaller vessels with attendant small hemorrhages. These lesions destroy the nervous parenchyma. These hemorrhagic and degenerative phenomena are particularly located around the ventricular system, and especially the basilar part of the third ventricle. This syndrome was first described by Wernicke [26] under the heading of polioencephalitis hemorrhagica superior and inferior. Alexander, Pijoan, and Myerson [2] have reproduced Wernicke's syndrome experimentally in pigeons by depriving them of vitamin B_1, while allowing them an ample supply of other vitamins.*

The Electroencephalograph in the Study of Alcoholism

The electroencephalogram is of definite value in the dynamic study of the effects of acute alcoholism. However, the electroencephalogram in chronic alcoholism (not associated with acute ingestion) has not been too helpful. Davis, Gibbs, Davis, Jetter, and Trowbridge [8] have shown that the electroencephalographic pattern was only slightly abnormal in a series of chronic alcoholics who were without evidence of neurologic disease and who were not intoxicated at the time the electroencephalogram was taken. They conclude ". . . alcoholics as a group, lie on the borderline as members of society, in that they cannot be classified as either normal or abnormal." Of course, if there are associated vascular disturbances or damage to the neuronal structures of areas accessible to the electroencephalograph, non-specific, focal changes may be noted. Just as with other types of narcotic drugs, the effect of alcohol may be traced with the electroencephalograph. As the stuporous stage is approached, the electroencephalographic pattern becomes slower, and assumes the character of a non-specific stupor record. The electroencephalogram corresponds more closely with the clinical state than it does with the blood alcohol level.

The Cerebrospinal Fluid in Acute and Chronic Alcoholism

Rosenbaum, Herren, and Merritt [21] studied the cerebrospinal fluid of 201 patients with chronic alcoholism who were admitted to the hospital in an acute exacerbation. The majority were admitted in coma. The abnormal findings in the cerebrospinal fluid from these patients with both chronic and acute alcoholism were confined almost entirely to an increase in pressure (25 per cent of 133 patients in whom reliable pressure measurements were made) and an increase in the total protein content (20 per cent of 127 patients in whom this procedure was carried out). These authors attributed the increased pressure to a combination of cerebral edema and dilatation of the cerebral vessels. The increase in the total protein content was somewhat more difficult to explain and they noted that "it is possibly due to an increased permeability of the choroidal and meningeal vessels to protein as a result of injury to the vessels by the alcohol and possibly to degenerative changes in the parenchyma and nerve roots produced by the alcohol." They concluded that the occurrence of any abnormality in the cerebrospinal fluid of alcoholics should make one seriously consider the possibility of the presence of other causes for the abnormality, such as subdural hematoma,

* See also: deWardener, H. E., and Lennox, B.: Cerebral Beriberi (Wernicke's encephalopathy), Lancet, 1:11-17 (Jan. 4), 1947.

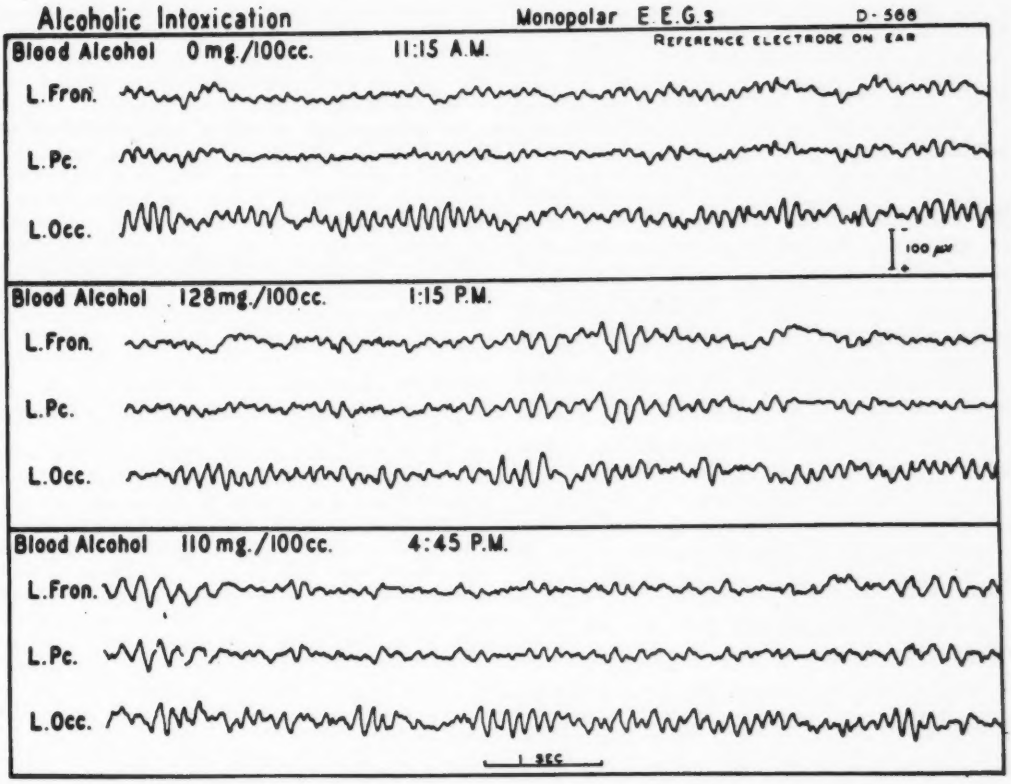

Fig. 2.—Electroencephalograms of one subject taken before drinking, and 1 and 3 hours, respectively, after finishing drinking. Note the 6 cycle episodes in the frontal and precentral records at 1:15 p.m. and at 4:45 p.m. (From Davis, Gibbs, Davis, Jetter, and Trowbridge, 1941.)

brain tumor, or syphilis of the central nervous system. Only after such conditions are excluded should the abnormalities in the cerebrospinal fluid be attributed to alcoholism.

Clinical Neurologic Syndromes Associated with Alcoholism

It is proposed to discuss only briefly the commoner clinical syndromes associated with the ingestion of alcohol over a long period of time. Little time will be devoted to the relatively common, acute syndromes including inebriation and acute psychoses.

It may be said that there are two main groups of clinical pictures, namely psychoses and neuritides. It is not unusual to find a combination of them in the same patient. This combination plus disordered innervation of the eyes produces the clinical picture that is called Wernicke's syndrome. If the brunt of the disease is borne by the peripheral nerves and spinal cord and not the brain, the picture is that of combined system disease not unlike that usually associated with pernicious anemia. The local degeneration of Purkinje cells in the cerebellum produces the syndrome of alcoholic cerebellar degeneration which has been so clearly described by Romano, Michael, and Merritt.[20] The concentration of lesions within the deep white matter, corpus callosum, and corona radiata produces the clinical syndrome described by Marchiafava and Bignami.

It is of considerable importance and therefore reiterated that almost any syndrome associated with chronic alcoholism may be duplicated by nutritional deficiency, for example, peripheral neuritis, combined system disease, and the psychoses of pellagra.

Alcohol and Epilepsy

The harmful influence of alcohol in epilepsy is well known. The Romans had a name for it—*morbus convivialis*. Some sections of this country are familiar with a syndrome known as rum fits. This syndrome is seen in individuals who are really epileptics, and whose convulsive episodes usually are associated with the ingestion of alcohol. In some patients the relationship is so clear that when alcohol is interdicted, no further fits occur. Rum fits usually make their appearance in the sobering-up period, 24 to 48 hours following the ingestion of alcohol. This suggests that the mechanism is related to that which occurs in delirium tremens, since fits and delirium tremens occur in this period when the brain presumably has undergone maximum swelling.

After questioning 1,254 epileptics over the age of 15 years, Lennox[12] reported that 26 per cent admitted the use of alcohol moderately and 6 per cent to excess. These figures are probably no different than those from control groups. In epilepsy, alcohol seemed to be a definite factor in the production of fits in 6 per cent of the entire group of 1,254 patients and in 21 per cent of those who admitted the use of alcohol. In the frequent users, 57 per cent reported that seizures sometimes followed indulgence. In the latter, Lennox reported that alcohol seemed to be a more potent factor in the production of fits in symptomatic epilepsy (that is, convulsions preceded by trauma or disease) than in constitutional or idiopathic epilepsy. Thus, it may be stated as a general rule that alcohol is a definite factor in the production of convulsions in an individual so predisposed, which would appear to require the interdiction of drinking in such individuals.

Delirium Tremens

Delirium tremens is an acute psychosis characterized by disorientation, hallucinations, apprehension, tremors, insomnia, and general signs of toxicity occurring in an individual with a history of prolonged alcoholism. The mechanism involved in the production of this syndrome has been mentioned above.

The mortality rate is reported as varying from nothing to 5 per cent. Therapy has been quite varied, and usually is aimed in two directions: to decrease cerebral edema, and to induce sedation. Therapy has included limitation of fluid, forcing of fluid, cerebrospinal fluid drainage, the routine use of digitalis, hypertonic sucrose or glucose solutions, vitamins orally and parenterally, and sedation of all types. In a series of 524 consecutive cases reported by Rosenbaum, Piker, and Lederer,[23] the mortality rate was 1.7 per cent. Their conclusions are of interest: ". . . regardless of what sort of treatment procedure is used, and so long as no measures are instituted which are actually injurious, adequate general medical and psychiatric care should serve to keep the mortality rate in uncomplicated delirium tremens down to a minimum." It was the feeling of these authors that an important consideration in their relatively low mortality rate was the efficacious use of superficial psychotherapy which included much attention and reassurance, as well as the feeling of confidence engendered in themselves by their persistently low mortality rate.

Peripheral Neuritis

The occurrence of peripheral neuritis in chronic alcoholism is a relatively common phenomenon. Invariably it is associated with the history of rather long-standing nutritional deficiency, and the clinical and pathologic syndromes produced are not unlike those seen in either beriberi or pellagra in which alcohol plays no rôle. Clinically the syndrome is characterized by multiple peripheral neuritis of symmetrical nature and usually most marked in the terminal portions of the extremities and worse in the lower than in the upper extremities. The sensory manifestations include spontaneous pain and paresthesias; typical glove and stocking hypesthesia of the skin are usually demonstrable, associated with tenderness of the deeper structures.

In pellagra not associated with alcoholism the incidence of neuritis is high as determined by clinical method. However, paralyzing polyneuritis as seen in alcoholism is practically non-existent, a feature which favors the theory of direct toxic action of alcohol on nerves.[25] In support of the nutritional deficiency hypothesis in alcoholism, it has been said that the paralytic polyneuritis associated with alcoholism represents the final stage of the long-standing process of deficient nutrition. The nerves have deteriorated gradually until the process has reached the point where it is no longer reversible; for recovery to occur, the nerve cell must form new axones.

In a histological study of peripheral nerves[4] it was demonstrated that myelin sheaths were reduced in number in the nerves of patients with pellagra; reduction was most marked in association with alcoholism. It is noteworthy that in those pellagrins who had been imbibing alcoholic liquors the damage to the nerves was much more severe. Study of morphologic changes in the peripheral nerves leaves much to be desired in the analysis of the syndrome of neuritis. Mild clinical signs may occur in the face of an apparently normal myelin sheath content of the nerve. At present the accurate diagnosis of minimal neuritis is difficult; deviation of the deep reflexes from normal is probably the most reliable single sign of peripheral neuritis. Spontaneous pain and muscle tenderness in the limbs may be present when the myelin sheath content of the nerve is normal.

Combined System Disease

The occurrence of subacute combined degeneration of the spinal cord associated with pellagra is well known. An identical picture may be produced in chronic alcoholism; invariably there is an associated nutritional deficiency. Again both the symptomatology and the pathology in the changes are more severe when there is the additional factor of alcoholism. Combined system disease is invariably associated with multiple peripheral neuritis. The clinical picture is not unlike the combined system disease which is most frequently found in association with pernicious anemia. Not infrequently there is an associated macrocytic anemia and achlorhydria. All forms of subacute combined degeneration of the cord respond well to adequate therapy with liver extract.

Korsakow's Syndrome

The combination of polyneuritis and a peculiar type of psychoses in an alcohol addict constitutes the syndrome described by Korsakow. In addition to the multiple symmetrical peripheral neuritis, the mental picture is characterized by confusion, disorientation, loss of more recent memory, and the tendency to confabulate. There is nothing specific

TABLE 2.—*Treatment Received by Fifty Patients with Korsakoff Psychosis. (From Rosenbaum and Merritt, 1939)*

Treatment	Status of Patient			
	Dead	Completely Recovered	Incompletely Recovered	Still in Institutions
No special therapy	11	5	3	3
Diet high in calories and vitamins	4	0	0	0
Diet high in calories and vitamins plus liver extract intramuscularly	7	3	3	4
Diet high in calories and vitamins plus vitamin B intravenously	0	4	1	2
Total number	22	12	7	9

about this mental state which may be seen in association with toxicities or with brain disease of many types. It is probably not too well recognized that the mortality rate in Korsakow's syndrome tends to be quite high. Marcus [14] reported mortality of 30 per cent, and the rate of complete recovery was 20 per cent. In the report by Marchand and Courtois [13] the outcome was fatal in 55 per cent. In the cases reported by Rosenbaum and Merritt,[22] the mortality was 44 per cent, and it was definitely higher for women than for men, and increased with age. Rosenbaum and Merritt concluded that "intensive dietary and vitamin therapy apparently is of great significance in regard to prognosis as to life and complete recovery." It is not the only factor, however, since 11 of the 22 patients who received no special therapy lived, but it was undoubtedly a life-saving measure in those severely afflicted patients who recovered.

Wernicke's Syndrome

Wernicke [26] described a disorder which he termed polioencephalitis hemorrhagica superior and inferior. It was notable for proliferation and varicose deformity of small vessels associated with small hemorrhages and subacute necrosis of the parenchyma, the lesions being located predominantly around the ventricular system and especially the basal part of the third ventricle. This syndrome has been produced in pigeons fed on a vitamin B_1 deficient diet though the birds were amply supplied with the other vitamins. It could not be reproduced experimentally with vitamin C deficiency. Clinically the syndrome is characterized by clouding of consciousness, ophthalmoplegias, pupillary disturbances, and peripheral neuritis. A galaxy of neurological and psychiatric phenomena may be present.

Marchiafava-Bignami Disease (Primary Degeneration of the Corpus Callosum)

This syndrome was first described by Marchiafava and Bignami in 1903, and there have been more than 50 cases reported in the literature. Up until 1936 all cases of the disease occurred in native Italians. The first American case was reported in 1937 in an Italian who had moved to Boston. The only occurrence in an individual of non-Italian stock was reported by Nielsen and Courville [18] in 1943. The pathologic findings are usually limited to necrosis of the mesial zone of the corpus callosum with sparing of the dorsal and ventral margins. The necrosis varies from softening and discoloration to cavitation and cyst formation. In the majority of cases the rostral portion of the corpus callosum is said to be affected first, and the more caudal regions later. In addition lesions of the anterior commissure, central semi-ovale, subcortical white matter, long association bundles, and middle cerebellar peduncles are not uncommon. The lesions tend to be bilaterally symmetrical and to spare the internal capsule, corona radiata, and the subgyral arcuate fibers. The gray matter is unaffected.

Clinically the disease seems to run a subacute to chronic course for three to six years. No case has been reported in which the diagnosis was made before death. The clinical picture consists of focal and general signs of cerebral disease, including mental symptoms which at times are extreme, convulsive phenomena, tremors, dysphasic disturbances, and

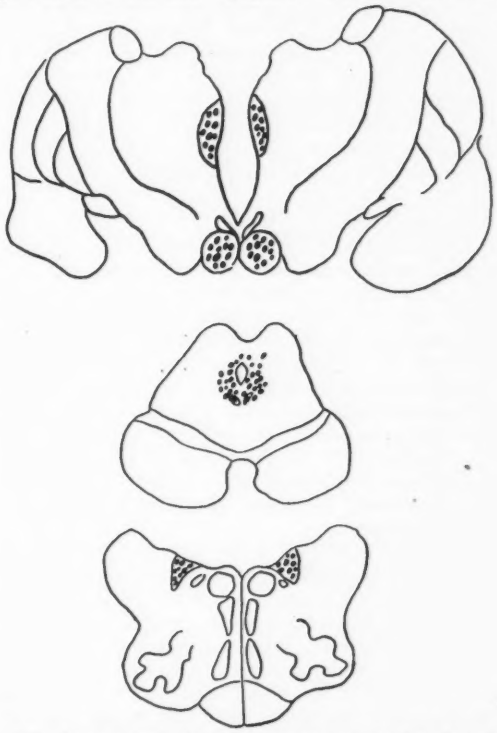

Fig. 3.—A schematic diagram showing the distribution of the lesions in Wernicke's disease. Note the lesions in the paramedian nuclei of the thalamus, in the mammillary bodies, in the periaqueductal region of the midbrain, and in the dorsal (pneumogastric) nuclei of the vagus. (From Alexander, L., Am. J. Path, 16:61-69, 1940.)

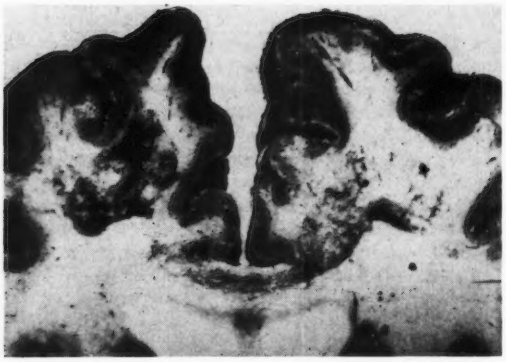

Fig. 4.—Marchiafava-Bignami's Disease. Section through anterior limb of internal capsule, showing extensive symmetrical lesions in subcortical white matter as well as in the corpus callosum. (From Merritt and Weisman, 1945.)

transient hemiparesis, and other motor disability. The occurrence of such symptoms in an elderly Italian male with a history of alcoholism, especially if he drinks Italian red wines should make one suspect this syndrome. The disease has never been seen in women. In the one non-Italian case reported by Nielsen and Courville, it is of interest to note that the patient was addicted to red wine. In those cases which have been carefully studied, there has been noted a gross dietary insufficiency which as Merritt and Weisman [15] point out may of itself lead to demyelination and necrosis of nervous tissue. The latter concluded that Marchiafava-Bignami disease "is considered a form of chronic alcoholic encephalopathy, for which an inadequate diet and prolonged alcoholism are necessary antecedents."

Alcoholic Cerebellar Degeneration

Alcoholic cerebellar degeneration has only recently been recognized; previously it had been described under the intracerebellar atrophies. Until 1933 only 14 cases had been reported. Since the appearance of the paper by Romano, Michael, and Merritt,[20] in 1940, the recognition of this disease has increased considerably. These authors showed quite definitely that alcohol or an associated nutritional deficiency or both were significant in the development of this syndrome, which resembled both clinically and pathologically the cerebellar disturbance previously described as cortical or intracerebellar atrophy.

The clinical picture is characterized by a slowly progressive cerebellar disorder beginning after middle age. In contradistinction to some other cerebellar syndromes there is no familial history of similar disturbance. The chief complaint is usually difficulty in walking, and on examination the signs of cerebellar deficit are symmetrical and most obvious in the lower extremities. The gait is stiff and the patient walks with the feet placed wide apart. Usually there is no nystagmus, but frequently there is dysarthria. Incoordination of the upper extremities is noted in some cases. Pathologically this syndrome is characterized by gross atrophy of the cerebellum, particularly the superior portion of the vermis and the quadrilateral lobule. On microscopy there is found a relatively absolute disappearance of the Purkinje cells of the cerebellum.

Neurologic Defects Associated with Contaminants of Alcohol

Alcohol frequently contains a denaturant. Here it is proposed to discuss briefly only two: triorthocresyl phosphate and methyl alcohol.

"Jake" Paralysis (Jamaica Ginger Palsy)

Jamaica ginger extract was used as an alcoholic beverage prior to March and April of 1930, when paralysis attributable to a denaturant in the extract appeared simultaneously in several localities throughout the country.[5] Jamaica ginger extract contains 70 per cent alcohol. The particular batches which produced the neurologic disease were adulterated with 2 per cent triorthocresyl phosphate.

The clinical syndrome of Jamaica Ginger Palsy was characterized by acute and severe gastrointestinal disturbances shortly after ingestion and by the appearance of multiple, symmetrical, generalized peripheral neuritis within seven to fourteen days. In chronic stages the picture was not unlike that of amyotrophic lateral sclerosis. Pathologically it was characterized by hyperplastic fibrosis of the small arteries and capillaries which apparently developed in the latent period (about 14 days) between the ingestion of the poison and the appearance of neurologic signs. The cresols whether ingested or applied to the skin eventually affect vessels. The degeneration in muscles and nerves as well as in the central nervous system may be related to a degree to the contiguously affected capillaries.

Methyl Alcohol and Optic Atrophy

During the late war, cases of methyl alcohol poisoning were reported associated with the drinking of "buzz bomb juice" and other non-standard alcoholic beverages which had been adulterated with methyl alcohol. The clinical picture is usually characterized by a rapid occurrence of blindness, with the associated pathologic picture of optic neuritis.

Treatment

In concluding we may allude briefly to treatment. It would seem unnecessary to note that alcohol must be interdicted in all of the disorders which have been mentioned. In almost any case the withdrawal may be performed abruptly if supportive therapy is attentive. The latter consists rather more of concern with nutrition than with sedation. The patient must receive adequate nutrition which is ideally administered in a thoroughly nutritious, well balanced diet. In any case probably it is well to reenforce the diet with vitamins, most effectively administered in intramuscular liver extract. If sedatives may not be avoided, paraldehyde is surely the drug of choice,

since its action is somewhat analogous to that of alcohol, and its margins of safety are quite wide.

Everyone is aware that the cure of alcoholism is difficult to attain. If the physician feels hopeful in this regard he should ask for the evaluation of his patient by a psychiatrist entirely familiar with the psychodynamics of alcoholism. Most able psychiatrists are wise enough not to attempt the *cure* of persons whose psychosexual development has been largely halted at infantile levels.

Even though cure may not be a goal, symptomatic relief may be feasible. In this field of endeavor the organization that has the name Alcoholics Anonymous has rendered a very great service indeed; it is only fair to say that the enlightened psychiatrist has sought the assistance of this group quite often for his alcoholic patients.

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NOTICES AND REPORTS

Woman's Auxiliary Reports on Year's Activities

Believing in the wisdom of the words of Dr. Stephen E. Gavin of Wisconsin, who recently told the women's auxiliary to the medical association in that state that "the wives of doctors are admitted to be the most powerful and tactful force between the medical profession and the public," the Woman's Auxiliary to the California Medical Association during the past year has exerted itself to expand and strengthen that force in California.

This was the keynote of the annual report which was delivered by Mrs. H. E. Henderson, president of the Auxiliary, to the C. M. A. at its 76th Annual Convention.

As evidence of the increasing recognition of the value of women's auxiliaries to medical associations, Mrs. Henderson noted that at the time of the American Medical Association convention in San Francisco last year, it was reported that the National Auxiliary's office was to be moved to the A. M. A. headquarters in Chicago and that the Trustees of the A. M. A. thereafter would meet with the Board of Directors of the Auxiliary to cooperate in planning the program of the Auxiliary.

Mrs. Henderson noted in her report that recognition already had been given "by the California Medical Association to its Auxiliary by its offer to print and mail our magazine, *The Courier*." The Auxiliary's president said that the members are "very proud of our bi-monthly magazine, which has a handsome cover in colors and about 14 pages of contents. We have received a number of compliments on it from other state auxiliaries."

Reporting on the organization of the California Auxiliary, Mrs. Henderson said that 802 members have been added in the past year, bringing the total to 3,116. The Auxiliary has local auxiliaries to 25 of the 40 county medical associations in the state, with membership ranging from ten in the smallest to 950 in the largest.

Reporting further on the county organizations, Mrs. Henderson said:

"In Los Angeles County there are now three branches, since the San Fernando Valley Branch of the Los Angeles County Medical Society has recently asked for an Auxiliary of its own, and an enthusiastic group of young women have organized there. If all the County Medical Societies took an equal interest, all their Auxiliaries would be strong. A few of the smaller ones are not. Merced Auxiliary has not recovered from its war difficulties and has not held a meeting for more than a year, so it is not now counted in our numbers. Tulare, Riverside, Ventura, and San Luis Obispo are struggling, principally for lack of encouragement and direction from their County Medical Societies. I do not say this in a spirit of censure, but because I wish to bespeak your help for them. San Bernardino County is the only large county which does not choose to have an Auxiliary. All the others are very active and we have had a wonderful growth in membership. One Auxiliary, that in Humboldt County, has a membership of 36 while its medical society has 37 members. This is a record which we all wish we might approach."

As to political activities, Mrs. Henderson said:

"We have been very much interested in legislation. San Diego and San Joaquin counties have had regular Study Groups on the subject, and Riverside has become a study group as a whole, its members making reports on national and state compulsory health insurance plans, on voluntary plans, and on the A. M. A. Ten-Point Program. All report programs at their regular meetings on some or all of these subjects, and local members are active in debates and programs of other women's groups. The chairman of the Pasadena Branch, Los Angeles County, has spoken more than 100 times to various groups against compulsory health insurance plans. Four County Auxiliaries helped their Medical Socities in active legislative campaigns last summer. Another has furnished arguments against the Warren plan to its Republican Central Committee and its

legislators. Sacramento and San Diego counties collected $1,375 in campaign funds from their doctors, and Alameda and Sacramento counties mailed out 91,500 pieces of campaign literature to patients over their doctors' signatures."

Mrs. Henderson said that at the suggestion of the Advisory Committee of the C. M. A., the Women's Auxiliary has "worked through our clubs, especially the Parent-Teacher Association, so that they would not again endorse the compulsory health insurance programs." As to the present attitude of the California Congress of Parents and Teachers, Mrs. Henderson said that through conversations with officials of that organization she has learned that they would be interested only in a health bill which would provide free physical examinations for all children. "Since the present [Warren plan] bill does not do this, they will take no action on it," the Auxiliary's president said. On the other hand, she said that "the California League of Women Voters has endorsed the policy of compulsory health insurance but does not approve the present bill because it does not go far enough."

In concluding her report on the political activities of the Auxiliary, Mrs. Henderson said: "I think I can safely promise that the members of the active Auxiliaries in this state will watch the actions of these organizations and do their best to influence them in what they think is the right direction."

Reporting on the efforts of the Auxiliary to collect money for the Medical Benevolence Fund, Mrs. Henderson said that she had received a report from the Auxiliary's Medical Benevolence chairman that "considerable ignorance of the meaning of Medical Benevolence has been encountered among doctors whose wives are not members of the Auxiliary and in doctors who are not married." The committee chairman further reported that although the Medical Benevolence Committee had taken for granted that the members of the C. M. A. were informed, "unfortunately this is anything but true."

The Auxiliary president said that she called this report to the attention of the C. M. A. "simply because I think perhaps you are unaware of this condition and will wish to do something to correct it."

"For total philanthropies," Mrs. Henderson continued, "the Auxiliaries have raised and donated over $6,000, including money for student loan funds, community chests, the various national health associations, the Red Cross, charity hospitals of several types, for the Public Health League, the Chaplain's Fund, Girl Scouts and children's camp funds, and for an audiometer for the schools of Santa Cruz County."

She concluded her report by presenting a check for $2,609 for the Medical Benevolence Fund.

In Memoriam

BLUM, STANFORD. Died in San Francisco, May 27, 1947, age 74, of a heart attack. Graduate of the University of California Medical School, Berkeley-San Francisco, 1896. Licensed in California in 1896. Doctor Blum was a member of the San Francisco County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

✤

LUTON, GEORGE ROSCOE. Died in Santa Barbara, May 19, 1947, age 67, after an illness of several months. Graduate of the Medical Faculty of Trinity University, Toronto, Ontario, 1904. Licensed in California in 1905. Doctor Luton was a member of the Santa Barbara County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

✤

MAGHY, CHARLES ALFORD. Died in San Diego, April 27, 1947, age 61. Graduate of the University of Illinois College of Medicine, Chicago, 1905. Licensed in California in 1920. Doctor Maghy was a member of the San Diego County Medical Society, the California Medical Association, and the American Medical Association.

✤

SMITH, LLOYD ERNEST. Died in Glendale, May 2, 1947, age 58, of a heart attack. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1925. Licensed in California in 1925. Doctor Smith was a member of the San Bernardino County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

NEWS and NOTES

NATIONAL • STATE • COUNTY

LASSEN

Plans are under way in the Tuberculosis Service of the California Department of Public Health to install a **tuberculosis case register** in the part-time health department of Lassen County. If this trial proves successful, case registers may be set up in other part-time health departments in the State.

LOS ANGELES

Dr. George V. Webster, Pasadena, who headed one of the Navy's plastic surgery units during the war, addressed the Pomona branch of the Los Angeles County Medical Society recently at the Pomona Valley Community Hospital, on the subject "Plastic Surgery of the Face as Seen in War and Civilian Life."

Appointment of **Dr. John N. Osburn** as chief surgeon for the Santa Fe Coast Lines Hospital at Los Angeles was announced recently by E. E. McCarty, chairman of the hospital's board of trustees. Dr. Osburn has been chief of the Eye, Ear, Nose and Throat Department at the hospital since 1924.

Dr. Richard P. Forinash, who during the war served in the Navy, has recently begun the practice of medicine in Lancaster where he is associated with Dr. W. R. Senseman in offices in the Community Hospital. Dr. Forinash is a graduate of the University of Tennessee Medical School.

MONTEREY

Dr. Margaret Swigert, for many years a practicing physician on the Monterey Peninsula, left recently for Holland where she is serving as a delegate to the **International Medical Women's Conference** in Amsterdam. En route, Dr. Swigert attended the centennial convention of the American Medical Association in Atlantic City.

ORANGE

"A very significant forward step was taken toward bringing much needed **hospital facilities** to Orange County," the Santa Ana Register reports, "when the board of directors of the Orange County Presbyterian Hospital met with the chief of the Bureau of Hospital Surveys, **Dr. Philip Gilman,** and Field Representative William Weeks, appointed by Governor Warren. These officials are now making a state-wide study of public health. Dr. Gilman was chosen for this investigation because of his wide knowledge of health conditions throughout the West, gained as clinical professor of surgery at Stanford University, as a captain in the United States Navy and as a past president of California Medical Association.

"Plans were formulated for an application for funds in excess of a quarter of a million dollars from federal and state appropriations now or soon to be made available. Further close cooperation was pledged by the State Bureau in helping to relieve the serious situation with reference to hospital accommodations in Orange County. The state officers said that plans locally had developed far beyond those in most California communities and praised the work of the board of directors of the proposed hospital which is to be located on a 20-acre site at Newport Beach."

SANTA CLARA

Dr. Douglas Wendt has recently opened an office for the practice of medicine at 1320 Lincoln Avenue in Willow Glen. He returned to San Jose last year following several years in the Army Medical Corps in France, Germany, the Philippines, and Japan. Dr. Wendt, who was graduated from Stanford University Medical School in 1937, interned at the San Francisco County Hospital and was a resident at the Santa Clara County Hospital.

SOLANO

Announcement was made recently by James S. Dean, state director of finance, that a 700-acre site near Vacaville was one of a half dozen in Northern California under consideration for the new $7,500,000 **state prison medical center.** Mr. Dean said two other sites near San Jose are under consideration but did not mention locations of the remaining suggested sites. An appropriation of $5,130,000 already has been made for the medical center, but according to Mr. Dean another $2,500,000 is needed to cover increased building costs.

GENERAL

Terms of the W. W. Norton Company medical **award for book manuscripts** written for the lay public by professional workers in the field of medicine have been altered slightly. Manuscripts may now be submitted at any time, the award not being limited to any one year. The Norton Award offers $5,000 as a guaranteed advance against royalties. Either complete manuscripts or detailed table of contents together with one hundred pages of manuscript may be submitted. Full details of the terms of the award may be secured by writing the publishers, W. W. Norton & Co., Inc., 101 Fifth Avenue, New York 3, N. Y.

Camp Whitaker, the **camp for diabetic children** between the ages of seven and seventeen which operates under the auspices of the University of California Medical School, will be operated again this year from August 3 to August 31. The camp is 60 miles east of Fresno at an elevation of 5,600 feet.

Sixty controlled juvenile diabetics on a regime which will not conflict with the camp program will

be accepted for each camping period. The full charge for a two-week camping period is $35. It is necessary that all applicants share as much of this expense as possible inasmuch as the number of children accepted will be limited by the funds available. Arrangements for special fees may be made through your clinic or the social workers of your county.

Application forms should be obtained from Dr. M. B. Olney, 1429 4th Avenue, San Francisco. Telephone inquiries should be made at SEabright 5113.

An affiliated **"Eye-Bank"** has been organized in **Boston** and is ready to serve the needs of New England. Seven hospitals in the Boston area and one in Maine have already become affiliated with it. The general public in New England is being urged to sign forms, available from the Boston Eye-Bank, indicating their willingness to donate their eyes for use after death.

The National Gastro-enterological Association announces award of first prize in its 1947 Prize Award Contest for the best unpublished contribution on Gastro-enterology or an allied subject has been made to **Dr. Frederic Duran-Jorda** of Manchester, England. Dr. Duran-Jorda's paper on "Histo-Pathology of the Semi-Squamous Epithelial Layer as Found in the Colon" was selected by the judges from amongst 12 entries received from all parts of the world. Certificates of Merit will be awarded to Drs. William Nimeh, Mexico City, D. F.; August Schrumpf and Trygve Kahrs, Porsgrunn, Norway; W. Paolino and G. Boccuzzi, Turin, Italy. The winning paper as well as those receiving Certificates of Merit will be published in the Review of Gastro-enterology, the official publication of the National Gastro-enterological Association.

Membership of the **National Mental Health Foundation** has grown to nearly 3,000 in its first year of existence according to a report issued by Harold Barton, executive secretary. The Foundation is making a drive for community participation through local organizations to tackle the problems of mental illness and mental deficiency, pointing up prevention in the former and effective training in the latter. It is engaged on a study of model legislation to be applied to both fields. One of its major objectives, however, is to improve the standards for attendant training and promotion of a professional organization of hospital and institution attendants.

Because many **physicians holding Indiana licenses** are outside the state and their mailing addresses are unknown, The Board of Medical Registration and Examination of that state has asked that attention be called to a recently passed Indiana law requiring **annual registration** of physicians. Registration this year must be made before the first day of September. The fee for registrants residing outside the state is ten dollars. Further information may be obtained from the Board of Medical Registration and Examination, K. of P. Building, Indianapolis 4, Indiana.

INFORMATION

Metopon Hydrochloride*†

In 1929 with the funds provided by the Rockefeller Foundation the National Research Council, through its Committee on Drug Addiction, undertook a coordinated program to study drug addiction and search for a non-addicting analgesic comparable to morphine. The principal participating organizations were the Universities of Virginia and Michigan, the United States Public Health Service, the Treasury Department's Bureau of Narcotics, and the Health Department of the State of Massachusetts, which brought together chemical, pharmacological and clinical facilities for the purposes of the study. Metopon is one of the many compounds made and studied in this coordinated effort.

Chemically Metopon is a morphine derivative; pharmacologically it is qualitatively like morphine even to the properties of tolerance and addiction liability. Chemically Metopon differs from morphine in three particulars: one double bond of the phenanthrene nucleus has been reduced by hydrogenation; the alcoholic hydroxyl has been replaced by oxygen; and a new substituent, a methyl group, has been attached to the phenanthrene nucleus. Studies made thus far indicate that pharmacologically Metopon differs from morphine quantitatively in all of its important actions: its analgesic effectiveness is at least double and its duration of action is about equal to that of morphine; it is nearly devoid of emetic action; tolerance to it appears to develop more slowly and to disappear more quickly and physical dependence builds up more slowly than with morphine; therapeutic analgesic doses produce little or no respiratory depression and much less mental dullness than does morphine; and it is relatively highly effective by oral administration.

In addition to animal experiments these differences have been established by extensive employment of the drug in two types of patients—individuals addicted to morphine, and others (terminal malignancies) needing prolonged pain relief but without previous opiate experience. In morphine addicts, Metopon appears only partially to prevent the impending signs of physical and psychical dependence. In terminal malignancy, administered orally, it gives adequate pain relief, with very little mental dulling, without nausea or vomiting and with slow development of tolerance and dependence.

The high analgesic effectiveness of oral doses (with the elimination of the disadvantage to the patient of hypodermic injection), the absence of nausea and vomiting even in patients who vomit with morphine or other derivatives, the absence of mental dullness and the slow development of tolerance and dependence place Metopon in a class by itself for the treatment of the chronic suffering of malignancies, and it is for that purpose exclusively that it is being manufactured and marketed.

Metopon will be available *only* in capsule form *for oral administration.* The capsules will be put up in bottles of 100 and each capsule will contain 3.0 mgm. of Metopon hydrochloride. They can be obtained by physicians only from Sharp & Dohme or Parke, Davis & Co., on a regular official Narcotic Order Form, which must be accompanied by a signed statement supplying information as to the number of patients to be treated and the diagnosis on each. The drug will be distributed for *no other purpose* than oral administration for chronic pain relief in cancer cases.

The dose of Metopon hydrochloride is 6.0 to 9.0 mgm. (2 or 3 capsules), to be *repeated only on recurrence of pain,* avoiding regular by-the-clock administration. As with morphine, it is most desirable to keep the dose at the lowest level compatible with adequate pain relief. Therefore, administration should be started with two capsules per dose, increasing to three only if the analgesic effect is insufficient.

Tolerance to any narcotic drug develops more rapidly with excessive dosage and under regular by-the-clock administration. Also, as a rule, the pain of cancer varies widely in intensity from time to time. Pain, therefore, should be the only guide to time of administration and dosage level. Tolerance to Metopon hydrochloride develops slowly. It can be delayed or interrupted entirely by withholding the drug occasionally for 12 hours or for as much of that period as the incidence of pain will permit.

To each physician will be sent a record card for each patient to whom Metopon hydrochloride is to be administered. He will be requested to fill out these cards and return them in the addressed return envelope. He must furnish this record of his patient and his use of Metopon hydrochloride if he wishes to repeat his order for the drug. The principal object of this detailed report is to check the satisfactoriness of Metopon hydrochloride administration in general practice. The physician's cooperation in making it as complete as possible is earnestly solicited.

The limited use of Metopon hydrochloride as described above has been recommended by the Drug Addiction Committee of the National Research Council and the Committee with the cooperation of the American Cancer Society, will supervise the distribution of the drug. The Committee is composed of Wm.

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* Methyldihydromorphinone hydrochloride.

† This article on Metopon Hydrochloride was prepared by the Committee on Drug Addiction, Division of Medical Sciences of the National Research Council.

Charles White, Chairman, Washington, D. C.; H. J. Anslinger, Commissioner of Narcotics, United States Treasury Department, Washington, D. C.; Lyndon F. Small, National Institute of Health, Washington, D. C.; and Nathan B. Eddy, National Institute of Health, Washington, D. C. Queries and comments on Metopon may be directed to Dr. Eddy, who will answer them for the Committee.

U.S. Bond Purchase Plan For Doctors Offered

The nation's banks, by arrangement with the United States Treasury Department, are offering to physicians and other self-employed individuals a systematic savings investment plan under which regular monthly deductions may be made from their checking accounts for the purchase of United States Savings Bonds.

Designed to meet the need of physicians for an orderly investment system requiring a minimum of supervision, the plan, which already is in operation, provides that a depositor who wishes to buy a bond each month has only to sign a card authorizing his bank to deduct from his checking account the purchase price of the bond in whatever denomination he chooses. Each month the bank delivers the bond to the customer, whose periodic bank statements show the deductions for payments.

The following table has been prepared by the Treasury Department to show the aggregate of savings and accumulated interest under the "Bond-A-Month Plan":

If you invest each month under the Bond-a-Month Plan	In five years you will have	In ten years you will have
$ 37.50	$ 2,319.00	$ 4,998.00
75.00	4,638.00	9,996.00
150.00	9,276.00	19,992.00
300.00	18,522.00	39,984.00

Letters to the Editor . . .

ASCORBIC ACID WITHHOLDING THERAPY

The possibility of controlling malarial infection by reduced intake of vitamin C (ascorbic acid) is suggested by McKee[3] and his co-workers of the Department of Comparative Pathology, Harvard Medical School.

During the course of malarial studies with monkeys, inoculated with *P. knowlesi,* the Harvard investigators inoculated seven monkeys with spontaneous vitamin C deficiency and an additional group of monkeys rendered deficient by previous feeding on Shaw's[4] ascorbic acid free synthetic diet. In control animals on normal diets containing adequate amounts of ascorbic acid there was usually a rapid increase in the number of parasites in the circulating blood, with death within six to seven days. In the ascorbic acid deficient animals there was only a slow rise in the percentage of parasites with a gradual spontaneous control of the infection. Intramuscular injection of 80-100 mg. of ascorbic acid into these animals was followed by a rapid increase in the number of malarial parasites, with death within two to six days.

The tests indicate that in monkeys a relatively high ascorbic acid titer of the blood stream is necessary for the rapid multiplication of the malarial plasmodium, low titers serving as an inhibiting mechanism. Whether or not this inhibiting action of vitamin C deficiency is due to a direct action on the parasites or to an indirect one through the animal host, is not yet determined. McKee is inclined to attribute it to an indirect action, since attempts thus far to demonstrate the need of ascorbic acid for the *in vitro* growth and multiplication of *P. knowlesi* have been inconclusive.

Studies by Marin,[2] Horvitt[1] and others suggest that the interrelationship between malarial parasites and ascorbic acid is the same in humans and monkeys. If so, ascorbic acid withdrawing therapy may be of future clinical interest.

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W. H. MANWARING, M.D.,
P. O. Box 51,
Stanford University, Calif.

BOOK REVIEWS

MENTAL MISCHIEF AND EMOTIONAL CONFLICTS. By William S. Sadler, M.D., F.A.P.A., Consulting Psychiatrist, Columbus Hospital; Fellow of the American Psychiatric Association, the American Medical Association, the American Association for the Advancement of Science; Member of the American Psychopathological Association. 1947. The C. V. Mosby Company, St. Louis.

That this 400-page volume is probably no worse than most works attempting to present modern concepts of nervous illness to the public is the best that can be said for it. There are portions of the book which, to the eye of the reader trained in this field, possess real merit. However, such a reader is no wiser for having read them, while the untrained reader certainly will be unable to discriminate between these passages and the many which are of doubtful value.

In essence, the book attempts to present, from the eclectic viewpoint, the whole gamut of functional nervous and mental diseases, from the standpoint of etiology, symptomatology, and treatment. The presentation is faintly reminiscent of the old fashioned "doctor book" which some of us can remember as occupying a high shelf in the bookcase of our childhood home. I am afraid it will prove equally unfruitful, if not actually dangerous, to its readers.

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FUNDAMENTALS OF CLINICAL NEUROLOGY. By H. Houston Merritt, M.D., Professor of Clinical Neurology, College of Physicians and Surgeons, Columbia University; Chief of Division of Neuropsychiatry, The Montefiore Hospital; Fred A. Mettler, M.D., Ph.D., Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University, and Tracy Jackson Putnam, M.D., Professor of Neurology and Neurological Surgery, College of Physicians and Surgeons, Columbia University. 1947. The Blakiston Company, Philadelphia. 96 Illustrations. 289 pages. Price $6.00.

This work can be termed a handbook in the practical sense that in a relatively small volume it includes those things which should be encompassed in the knowledge of the general practitioner of medicine regarding the specialty of neurology. It fills a definite need for a text which may be recommended to the medical student on his first contact with clinical neurology, yet will not be outgrown by him even though he should ultimately come to specialize in the field.

The mechanics of the neurological examination is very well covered. There is perhaps more detailed stress on anatomical relationships not too clearly related to the clinical pictures presented; some of this complexity is certainly due to the widespread use of diagrams from a text on neuroanatomy by one of the authors which goes far beyond the clear and simplified presentation provided by this book.

The volume is well bound in a water-resistant cover. The type face and paper are excellent; it is a pity that current standards of workmanship allowed at least the copy seen by this reviewer to be badly smudged with ink in a number of places.

A SURGEON'S DOMAIN. By Bertram M. Bernheim, M.D., Associate Professor of Surgery at The Johns Hopkins Medical School and Visiting Surgeon to The Johns Hopkins Hospital. W. W. Norton & Company, Inc., New York. Price $3.00.

The author, an Associate Professor of Surgery at Johns Hopkins Medical School, dramatizes in this book the many problems that arise during the teaching and training of young surgeons. He emphasizes the hazard to the patients of poorly done surgery and makes a rosy picture of the surgeon's artistry and skill as it is evidenced in a perfectly performed operation.

The political complexities of staff and hospital management which exist everywhere are laid wide open.

The nurse problem, which is now quite acute and will require more consideration as time moves along, the author feels can be solved by less rigid requirements and more pay for student nurses. Those nurses with good educational background and qualifications should be advanced to higher grades of standing and compensation. They might, in a way, assume some of the duties of internes.

The author proposes the institutionalizing of well qualified surgeons, which he feels will enhance the standing of the profession and promote for the patients a healthier concept of indications and technique in the performance of surgical operations. This arrangement exists now in a few instances where full time faculties occupy medical schools. Dr. Bernheim evidently wishes the same procedure for all hospitals.

The author calls attention to the turmoil and unhappiness that envelopes the very well trained young surgeon embarking upon the Sea of Free Enterprise. Many fall into the trap of fee division which evidently exists more or less in various communities. It is an unhealthy situation and should be actively attacked by all agencies. Perhaps one can agree with him that the road can be made easier by the government gliding such a well trained man into an institution established in an out-of-the-way community, subsidized for the purpose of better medical care. This may be on the way right now.

This book will be found interesting in many particulars to all doctors and their patients.

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EXPERIENCES WITH FOLIC ACID. By Tom D. Spies, M.D., Associate Professor of Medicine, University of Cincinnati School of Medicine, Director of the Nutrition Clinic, Hillman Hospital, Birmingham, Alabama. 110 pages. Illustrated. 1947. The Year Book Publishers, Inc., Chicago. Price $3.75.

This is a monographic review of the work recently done on folic acid and of the work done generally on macrocytic anemias by Spies and his collaborators. It is written in a chatty, entertaining, journal-

istic style by an enthusiast who vents his ideas and opinions with the gusto of a father describing his first born male child. If it is not a rigidly scientific manuscript, it is interesting as the revelation of an active, restless mind which jumps from point to point in the narrative even as the author has scrambled from rock to rock in his quest among the macrocytic anemias.

The first half of the monograph deals with the study of macrocytic anemia in general. The latter half is concerned with folic acid. The impression conveyed is summarized by the statement (on page 46) that of 218 persons who received folic acid "every person with Addisonian pernicious anemia, sprue, nutritional macrocytic anemia, macrocytic anemia of pregnancy and nutritional leukopenia has responded satisfactorily." One has to read another 30 pages before he finds out that combined system disease not only fails to regress but may actually develop while the patient is receiving folic acid. It therefore is not a substitute for liver extract but at present actually is harmful unless given under controlled experimental conditions. One may mention, too, that other investigators have not had the author's uniformly happy hematological response in non-tropical sprue.

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PRINCIPLES AND PRACTICE OF OBSTETRICS. By Joseph B. DeLee, M.D., and J. P. Greenhill, M.D. Ninth Edition, with 1108 illustrations on 860 figures, 211 in color. W. B. Saunders Company, Philadelphia. 1947. Price $10.00.

This grand old text has been revised extensively by Dr. J. P. Greenhill, who for many years was a close associate of the late Doctor DeLee. Doctor Greenhill edited the previous edition with pious respect for the departed author without making major changes. In the present edition he has dropped much that had become traditional and outmoded and added considerable material in line with progress in the fundamental and clinical sciences. A number of the old chapters have been rewritten in their entirety; several new chapters have been added. The present edition has been enhanced by many new illustrations cleverly designed to help the beginner in visualizing difficult problems.

Analgesia and anesthesia has been brought up-to-date in text and graphic depiction of technical matters. Methods are compared critically in regard to safety and hazards. This chapter condenses much useful and basic information into relatively few pages, making it easy for the busy practitioner and overworked student to acquire basic knowledge with a minimal amount of reading. Fetal erythroblastosis and the Rh factor actually can be read with profit and enjoyment, having been boiled down to essentials without obscuring the subject matter with highly technical descriptions. The chapters dealing with various aspects of physiology are well illustrated and the respective discussions deal with a difficult subject in a manner that should please teacher and student alike and even might entice the busy practitioner to revise old notions. The various chapters dealing with the architecture of the pelvis and its bearing on the mechanisms of labor are a bit disjointed, as they are in most obstetrical texts, but they contain much useful information, though the reviewer would have welcomed a more extensive discussion of the comparative value of radiographic and manual pelvimetry. However, salient factors in pelvic architecture and their bearing on labor are reviewed in the light of traditional as well as anthropomorphic values so that the observant student can equip himself adequately for a better understanding of the normal and abnormal mechanism of labor.

Doctor Greenhill has enhanced the value of chapters describing the various disease processes encountered in pregnancy by adding newer conceptions of their etiology and their treatment. Chapters covering normal pregnancy and labor essentially were left unchanged. Operative obstetrics are illustrated in detail, including the newer techniques of extraperitoneal cesarean section. Much of the treatment described in the various chapters is based on experience at the Chicago Lying-In Hospital. A more extensive discussion of proven methods used elsewhere would have enhanced the value of therapeutic matters. However, this purely is the personal reaction of the reviewer and in no way is meant to belittle the splendid job done by Doctor Greenhill in perpetuating one of the great textbooks of obstetrics.

* * *

PRACTICAL PHYSIOLOGICAL CHEMISTRY, Twelfth Edition. By Philip B. Hawk, Ph.D., President, Food Research Laboratories, Inc., Long Island City, New York; Bernard L. Oser, Ph.D., Director, Food Research Laboratories, Inc., Long Island City, New York, and William H. Summerson, Ph.D., Associate Professor of Biochemistry, Cornell University Medical College, New York City. Copyright 1947. The Blakiston Company, Publishers, Philadelphia. Price $10.00.

The present edition, appearing 40 years after the first and ten years after the most recent edition, exemplifies the growth and present state of physiological chemistry. Its well-printed and well-bound 1,323 pages contain directions for carrying out almost every qualitative or quantitative chemical analysis likely to find a place in medicine.

Many modern devices and their applications are discussed: the polarograph, electrophoresis apparatus, photoelectric colorimeter, flame photometer, photoelectric quartz spectro-photometer, photofluorometer, and mass spectrometer, each recieve attention. There is a section on isotopes, and a chapter on antibiotics and metabolic antagonists; the 17-ketosteroids are included.

There appear to be few shortcomings. Urinary casts are described, but the chemical properties causing the disappearance of hyaline casts from dilute or alkaline urine receive no attention. Methods are not given for the determination of substances used in the measurement of glomerular filtration rate or renal plasma flow. Watson's simple test for the detection of porphobilinogen in the urine is omitted. In many places, interpretations of the results of chemical analyses leave much to be desired.

These are all minor matters, easily forgiven. The chapter on gastric analysis, however, is a dismal, obsolete one far below the otherwise high standards of this edition.

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PENICILLIN THERAPY, Including Streptomycin Tyrothricin and other Antibiotic Therapy. By John A. Kolmer, M.D. Second Edition. D. Appleton-Century Company, New York. Price $6.00.

The fact that Doctor Kolmer's book on penicillin and other antibiotics now goes into a second edition shows how rapidly progress is being made in this domain. Doctor Kolmer covers the subject systematically. There are general chapters on the principles of chemotherapy, and the history of penicillin and methods of production are described. Methods of assay, chemical and physical properties are then dealt with, and finally the details of clinical application are discussed. Streptomycin and other antibiotics are dealt with more briefly in the concluding chapters. The book is useful because of attention to detail and the thorough bibliographies. In a quickly moving subject it is impossible to keep entirely up-to-date in any book, but essential matters are unchanged for the most part and this treatise is certainly a storehouse of valuable information on the whole subject.

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PARENTERAL ALIMENTATION IN SURGERY, With Special Reference to Proteins and Amino Acids. By Robert Elman, M.D., Associate Professor of Clinical Surgery, Washington University School of Medicine, St. Louis, Missouri. Paul H. Hoeber, Inc. Price $4.50.

This monograph comes at a timely moment, as the subject of parenteral feeding and support of the patient has made great strides in the past few years. Doctor Elman first covers the interesting historical phase of this subject, then he considers the six major nutritional substances separately. The general indications and methods of administration are adequately covered.

Following this are chapters devoted to more detailed study of water, electrolyte, energy, vitamin and protein needs. The largest part of the book is devoted to the latter, and the subject is rather exhaustively covered. Special emphasis is placed on the use of protein hydrolysates as a source of available nitrogen. One chapter is devoted to a practical program for parenteral administration.

In discussing the use of fluids to hydrate a patient, the author confuses the reader as to the merits of 5 per cent dextrose and normal saline. On page 90 he states that five liters of 5 per cent dextrose actually dehydrates while the same volume of saline hydrates the patient. On page 65 he states that dehydration from water deprivation alone should be corrected by dextrose and amino acids with only 1 or 2 grams of salt per liter. Clarification of such views would be helpful.

The author discusses and recommends the use of plasma as one source of protein, but he fails to caution the practitioner about the great danger of homologous serum hepatitis. This threat is so great that many physicians use plasma sparingly.

A chapter on the use of alcohol intravenously as an additional source of calories as well as a sedative could be added at a revision of the text.

This monograph is well printed on paper that is better than the usual postwar product, but which is nevertheless of only fair quality. Figures and tables are adequate. The bibliographies at the end of each chapter are outstanding.

Finally, the name of the book should be changed to a more general title. While parenteral fluids and nutritives are important in surgery, they are equally so in medicine, pediatrics, psychiatry, etc., and this volume should be of as great value to the internist as to the surgeon.